FORMULATION AND EVALUATION OF LEVOFLOXACIN ORAL DISPERSIBLE TABLETS

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Submitted By

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Under the Guidance of

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CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF LEVOFLOXACIN ORAL DISPERSIBLE TABLETS"** submitted by **PUNITHA.D (Reg No.261311055)** in partial fulfillment of the Degree of Master of Pharmacy in Pharmaceutics of The Tamil Nadu Dr.M.G.R Medical University, Chennai at Annai Veilankanni's Pharmacy College, Chennai- 600 015 is the Bonafide work carried out by her under my guidance and supervision during the academic year 2014-2015. The dissertation or any part of this has not been submitted elsewhere for any other Degree.

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Her conduct during this period was good and we wish his all success in future endeavors.

For INTERMED, CHENNAI

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DECLARATION

I hereby declare that the dissertation work entitled **"*FORMULATION AND EVALUATION OF LEVOFLOXACIN ORAL DISPERSIBLE TABLETS*"** is based on the original work carried out by me in Annai Veilankanni's Pharmacy College, Chennai and Formulation R&D INTERMED, CHENNAI under the guidance of **Dr. M. Senthil Kumar., M.Pharm., Ph.D., Principal** for submission to the Tamilnadu Dr. M.G.R. Medical University in the partial fulfilment of the requirement for the award of Degree of Master of Pharmacy in Pharmaceutics. The work is Original and has not been submitted in part or full for any other diploma or degree of this or any other university. The information furnished in this dissertation is genuine to the best of my knowledge and belief.

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Date : 05/08/2015
Place : Chennai

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LIST OF ABBREVIATIONS

ODT	Oral disintegrating tablet
FDT	Fast dissolving tablet
GIT	Gastro intestinal tract
WOW	Without water
WHO	World health organization
HPMC	Hydroxy propyl methyl cellulose
IR	Infra red
SR	Sustained release
DSC	Differential scanning colorimetry
Q.S.	Quantity sufficient
PVP	Poly vinyl pyrrolindrone
w/w	weight/weight
Gms	Grams
Rpm	Revolution per minute
SEM	Scanning electron microscopy
MG	Milli gram
MCG	Micro gram
LBD	Loose bulk density
TBD	Tapped bulk density
RH	Relative humidity
I.P.	Indian pharmacopoeia
Fig	Figure
ICH	International council of harmonization
SSG	Sodium starch glycolate
CP	Crospovidone
CCS	Croscarmellose sodium
MSC	Microcrystalline cellulose
MS	Magnesium stearate

I. INTRODUCTION

Oral disintegrating tablets are solid single unit dosage forms that are placed on tongue, allowed to disperse or dissolve in saliva without the need of water, frequently releasing of the drug for quick onset of action. Oral disintegrating tablets are well accepted by wide range of population especially as pediatric and geriatric patients who have difficulty in swallowing of conventional dosage forms. Some drugs are absorbed from mouth, pharynx and esophagus as saliva passes down to stomach. The bioavailability of such drug will be increase due to first pass metabolism[1].

Consumer satisfaction is the buzzword of the current millennium, and movement to achieve it has already begun in the pharmaceutical industry. An inability or un willingness to swallow solid oral dosage forms such as tablets and poor taste of medicine are some of the important reasons for consumer dissatisfaction.

Recent developments in technology have presented viable alternatives for the patients who may have difficulty in swallowing tablets or liquids. Traditional tablets and capsules administered with an 8-oz. glass of water may be inconvenient or impractical for some patients. For example a very elderly patient may not be able to swallow a daily dose of tablets. An eight year old child with allergies could use a more convenient dosage form of antihistamine syrup. A schizophrenic patient in the institution setting can hide a conventional tablet under his or her tongue to avoid his/ her daily dose of atypical antipsychotic. A middle-aged women undergoing radiation therapy for breast cancer may be too nauseous to swallow her H_2-blocker[6].

To overcome these drawbacks, Orally disintegrating tablets (ODT) or Fast Dissolving Tablets (FDT) has emerged as alternative oral dosage forms. These are novel types of tablets that disintegrate/dissolve/ disperse in saliva within few seconds. According to European Pharmacopoeia, the orally dispersible tablet should disperse/disintegrate in less than three minutes. The basic approach used in development of FDT is the use of super disintegrants like Crospovidone (Polyplasdone XL-10), Sodium starch glycolate (Primo gel, Explotab) and Pregelatinized starch (Starch-1500) etc., which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva.The bioavailability

of some drugs may be increased due to absorption of drugs in oral cavity and also due to pre gastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets[7].

Over the past three decades, ODT have gained much attention as a preferred alternative to conventional oral dosage forms such as tablets and capsules. ODTis a solid dosage form that disintegrates and dissolves in the mouth (either on or beneath the tongue or in the buccal cavity) without water within 60 seconds or less[8]. The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines in the Orange Book an ODT as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue. The European Pharmacopoeia however defines a similar term, that is fast dissolving tablet is a tablet that can be placed in the mouth where it disperses rapidly before swallowing[9].

These tablets are distinguished from conventional sublingual tablets, lozenges, and buccal tablets which require more than a minute to dissolve in the mouth. In the literature, FDT are also called orally disintegrating, orodisperse, mouth-dissolving, quick-dissolve, fast-melt, and rapid-disintegrating tablets and freeze-dried wafers.FDTs release drug in the mouth for absorption through local oro mucosal tissues and through pregastric (e.g., oral cavity, pharynx, and esophagus), gastric (i.e., stomach), and postgastric (e.g., small and large intestines) segments of the gastrointestinal tract (GIT). Conventional oral dosage forms refers to tablets and capsules that must be swallowed with water for dissolution, release, and absorption of the drug in the stomach and GIT distal sites.

Recent market studies indicate that more than half of the patient population prefers FDTs to other dosage forms and most consumers would ask their doctors for ODT (70%), purchase FDTs (70%), or prefer FDTs to regular tablets or liquids (>80%). These responses may, in part, be attributed to know ODT advantages such as ease of administration, ease of swallowing, pleasant taste, and the availability of several flavors. ODT also offer clinical advantages such as improved safety and in

some cases, improved efficacy and other broader indications[10]. FDT products have been developed for numerous indications ranging from migraines (for which a rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia.

Dozens of FDT products have been launched worldwide over the past decades. All through these products have the Common characteristic of quick disintegration and dissolution when placed in the mouth in the presence of saliva, their physical attributes vary. For example, several techniques for making compressed tablets (e.g., Dura Solv, CIMA Labs, Eden Prairie, MN; Ora Solv, CIMA Labs; and WOWTAB, Yamanouchi, Norman, OK) that are easy to handle and can be packaged in blister packs or bottles. In contrast, some lyophilization manufacturing processes (e.g., Zydis, Cardinal Health, and Dublin, OH) produce fragile freeze-dried tablets and compressed multi particle tablets that can be packaged only in unit-dose blisters because of their high friability.

The administration of FDTs may not inherently result in a faster therapeutic onset, but it can circumvent problems such as difficulty in swallowing traditional solid oral dosage forms, particularly by paediatric and geriatric patients. Since FDTS dissolve quickly, they cannot provide controlled or sustained release, except those that contain slow-dissolving, microparticulate-coated drugs, which quickly disperse and are swallowed[5]. Fast dissolve tablets are in demand now-days because of their ability to release the medicament in fraction of minutes. There are particularly useful for treatment of conditions like hypertension and arthritic pain for obvious reasons[11].

Many patients find in difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy[6]. The aim of novel drug delivery system (NDDS) is to enhances safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance; one such approach is “fast dissolving tablets”[12-15]. Fast dissolving tablets are gaining importance as a potential drug delivery system. This dosage form dissolves and disintegrates in the oral cavity within minutes without need of water or chewing. This

formulation is useful in administration of drug in pediatric, geriatric patients and also in patients suffering from chemotherapy induced nausea and vomitting[16].

Most of the marketed fast dissolving tablets consists of non-steroidal anti-inflammatory drugs e.g. Rofecoxib, Ketoprofen and anti hypertensive drugs e.g. Atenolol, Metoprolol, anti emetic drugs e.g. Ondansetron, Granisetron.Disintegrants can help to facilitable drug dissolution and subsequently improvement in bioavailability. Though starch is a good disintegrant it has some problems e.g. high levels required in formulation lack of compressibility which weakens the tablet structure[16]. Therefore, the need of development of a new disintegrant arises which eliminates all disadvantages that starch has. A number of disintegrants, known super disintegrants like sodium starch glycolate (Explotab), crospovidone (Polyplasdone XL), pregelatinized starch(Starch 1500) markedly improve tablet disintegrantion by swelling and or capillary action, cause tablet to break into fragments[17].The efficiency of these super disintegrants in any fast dissolving dosage forms depend on its selection, concentrations methods of incorporation and steps used for preparation.

Fast dissolving drug delivery is rapidly gaining acceptance as an important new drug delivery technology[18, 19]. Not all fast dissolving technologies actually dissolve; some use different disintegrants[13, 20] and / or effervescent agents that cause the dosage form to disintegrate rapidly in the patients mouth within a minute and can be gulped easily without the need of water. Thus, it offers increase patients compliance and convenience. Patient convenience and compliance oriented research has resulted in bringing out many safer and newer drug delivery systems. Fast dissolving tablet is one such example with increased consumer choice, for the reason of rapid disintegration or dissolution self-administration even without water or chewing [21-23].

ORAL DISINTEGRATING (OR)FAST DISSOLVING TABLETA REVIEW

Definition

United States food and Drug Administration (FDA) defined Oral Disintegrating tablet (ODT) as “A solid dosage form containing medical substance or

active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue[24], prepared by direct compression method. "The disintegration time for ODTs generally ranges from several seconds to about a minute.

These are also known as melt-in-mouth tablets, repimelts, porous tablets, oro-dispersible, quick dissolving or rapid disintegrating tablets.

Advantages of fast dissolving drug delivery system[25]

- Ease of administration to patients who refuse to swallow a tablet, such as paediatric and geriatric patients, mentally ill, disabled and uncooperative
- Convenience of administration and accurate dosing as compared to liquids
- No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water
- Good mouth feels property of FDTs helps to change the basic view of medication as "Bitter pill", particularly for pediatric patients
- Ability to prove advantages than solid dosage form
- Rapid dissolution of drug and absorption, which may produce rapid onset of action
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs in increased
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects (Figure No.1)

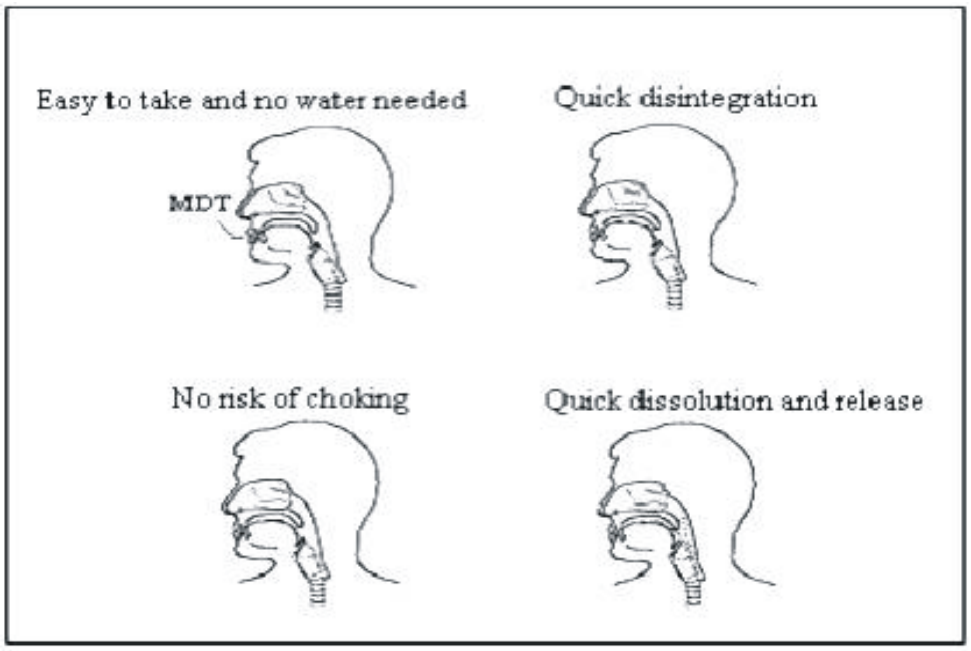


Figure No.1: Diagram showing advantages of FDTs[26]

Characteristics of fast dissolving drug delivery systems[27]

a. Ease of administration

FDT are easy to administer and handle hence, leads to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (Tablets and capsules) because of tremors of extremities and dysphagia. Fast dissolving delivery systems may offer a solution for these problems.

b. Taste of the medicament

Orodispersible delivery systems usually contain the medicament in taste-masked form. These delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.

c. Mouth feel

Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a products (Table No.1).

Table No.1: Various therapeutic areas in which the Fast dissolving dosage forms are available[27]

S.No	Target population	Therapeutic areas
1	Paediatric	Antibiotics Anti-asthmatics Cough/cold/Allergy Anti-epileptics Analgesics/Antipyretics Antidepressants
2	Adult and Elderly	Parkinson's Antimigraine Alzheimer's Anti-emetics Cancer Diabetes AIDS Gastric Relief Psychotherapeutics Cardiovascular Cough/ Cold/ Allergy Analgesics/ NSAIDS

INGREDIENTS COMMONLY USED IN FAST DISSOLVING TABLETS

Super disintegrants[28]

Use of disintegrants is the basic approach in development of FDTs. Disintegrants play a major role in the disintegration and dissolution of FDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates(Table No.2).

Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, whereas if concentration of superdisintegrant is above critical concentration, the disintegration time remains almost constant or even increases.

Sodium starch glycolate, Ac-di-sol (croscarmellose sodium), crospovidone, microcrystalline cellulose, pregelatinized starch are some of examples of super disintegrants.

Table No.2: Popular Disintegrants used in Tablet

S. No	Disintegrants	Mechanism	Concentration % w/w
1	Starch	Disintegrate forms pathways throughout the tablet matrix that enable water to draw into the structure by capillary action, thus leading to disruption of tablet.	5-20
2	Pregelatinized starch	Responsible for increased dissolution rate from this tablet is rapid disintegration due to superior swelling capacity.	5-15

S. No	Disintegrants	Mechanism	Concentration % w/w
3	Sodium Starch Glycolate (Explotab and Primogel)	Involves rapid absorption of water leading to an enormous increase in volume of granules result in rapid and uniform disintegration.	1-3
4	Cross-linked polyvinyl Pyrrolidone (Cross Povidone, CrosspovidonM, Kollidon, Polyplasdone)	The capillary activity of cross povidone for water is responsible for its tablet disintegration property.	0.5-5
5	Cellulose (Ac-Di-Sol, Nymce ZSX, PrimelloseSolutab)	They show their ability to swell on contact with water results in rapid tablet disintegration.	1-3
6	Microcrystalline Cellulose (Avicel)	Allowing water to enter the tablet matrix by means of capillary pores, which break the hydrogen bonding between adjacent bundles of cellulose microcrystals and exhibit very good disintegrant property.	10-20
7	Alginates (Alginic Acid, Satialgine)	High affinity for water absorption and high sorption capacity make it an excellent disintegrant.	1-5
8	Soy polysaccharides (Emcosoy)	Natural super disintegrant, Rapid swelling in aqueous medium or wicking action. Does not contain any starch or sugar. Used in nutritional products.	5-15
9	Gums (Guar Gums, Gum Karaya, Agar, Gellan Gum)	As disintegrants because of their tendency to swell in water	3-8
10	Chitin and Chitosan	Moisture sorption and water uptake was found the major mechanism of disintegration while dissolution related to swelling capacity	1-5

S. No	Disintegrants	Mechanism	Concentration % w/w
11	Smecta	Their layered leaves like structure consist of aluminium and octahydral layers sandwiched between two tetrahydral silica layers. It has a large specific area and high affinity for water makes it good disintegrant.	5-15
12	Isapghula Husk	Plantago ovata seeds husk has high swellability and gives uniform and rapid disintegration.	5-15
13	Polacrillin Potassium	It swells up at very fast rate upon contact with water or gastro intestinal fluid and act as an effective tablet disintegrant.	10-20
14	Ion Exchange Resins Ambrelite IPR 88, Indion, Doshion	Resins have ability to swell in the presence of water, showed disintegration of tablet.	0.5-5
15	Gas–Evolving disintegrants (Citic Acid, Tatric Acid, Sodium Bi Carbonate)	These react in contact with water to liberate carbon dioxide that disrupts the tablet.	>10%

Sugar based excipients[29]

Sugar based excipients are used for taste masking and as bulking agents. Most of the drugs are having unpleasant or bitter taste. And the basic requirement for designing FDTs is that the drug should not have disagreeable taste. So taste masking is necessary in most of the cases. Sorbitol, mannitol, xylitol, dextrose, fructose etc. are mainly used. Aqueous solubility and sweetness impart a pleasing mouth feel and good taste masking. But not all sugar-based materials have fast dissolution rate and good compressibility or compactability. However technologies are developed to make use

of the sugar based excipients in the design of fast dissolving tablets other ingredients commonly used are water soluble diluents, lubricants, plasticizers, binders, colors are flavors.

Mechanism of action of superdisintegrants

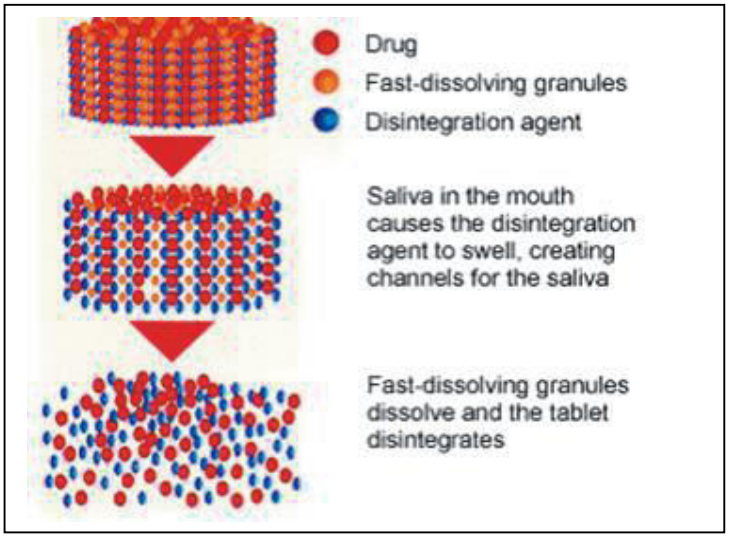


Figure No.2: Mechanism of action of superdisintegrants[5]

By capillary action

Disintegration by capillary action is always the first step. When the tablet is placed into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. For these types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

By swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling the tablets with high porosity, show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing

fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again shows down (Figure No.3).

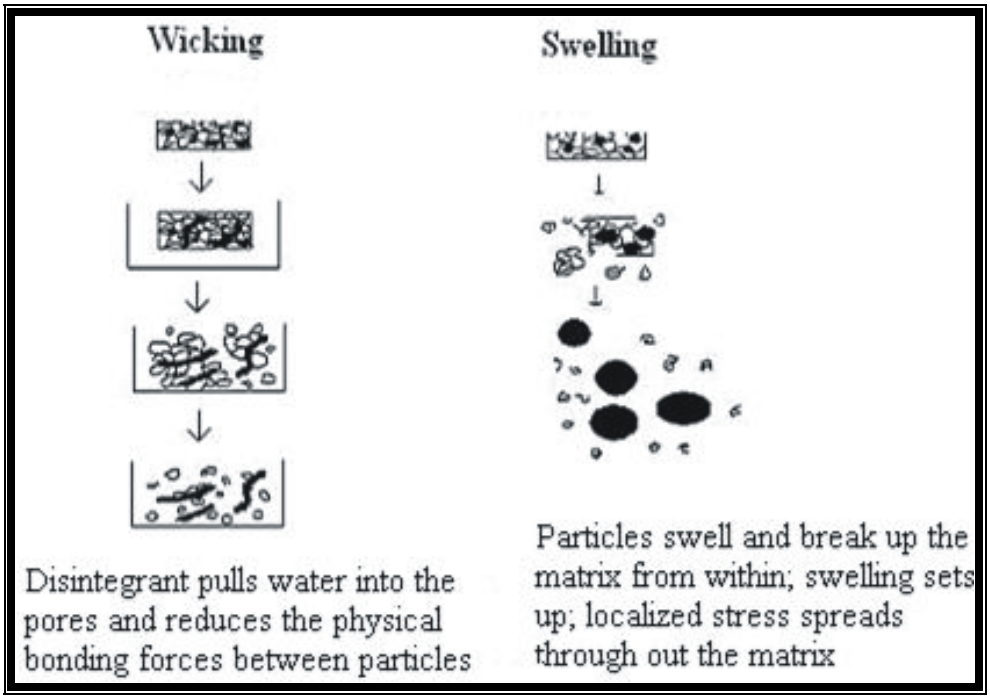


Figure No.3: Disintegration of Tablet by wicking and swelling[26]

By air expansion

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegration agents.

Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the

tablets. The effervescent blend is either added immediately prior to compression or can be added onto two separate fraction of formulation.[26]

By enzymatic reaction

Enzymes presents in the body also act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to accelerate absorption of water leading to an enormous increase in the volume of granules to promote disintegration.[29]

Due to particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with non-swellable disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking[13](Figure No.4).

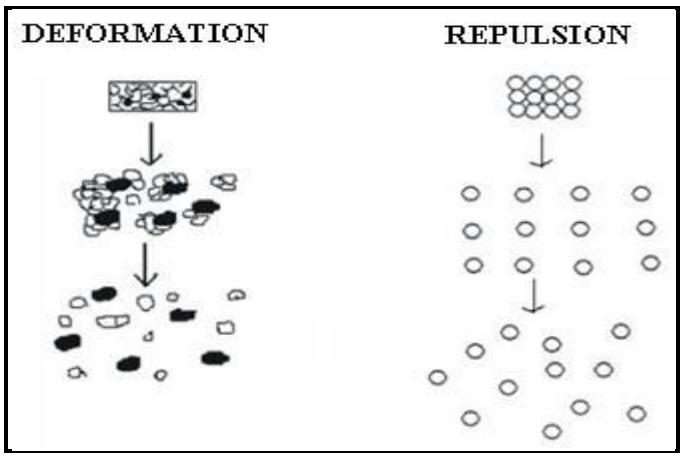


Figure No.4: Disintegration by Deformation and repulsion[5]

Due to deformation

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come

in contact with water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch as a superdisintegrant (Figure No.4).

CRITERIA FOR FAST DISSOLVING DRUG DELIVERY SYSTEM

An ideal FDT should possess the following properties[29]

- ✓ Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds
- ✓ Have a pleasing mouth feel
- ✓ Have an acceptable taste masking property
- ✓ Be harder and less friable
- ✓ Leave minimal or no residue in mouth after administration
- ✓ Exhibit low sensitivity to environmental conditions (temperature and humidity)
- ✓ Allow the manufacture of tablet by using conventional processing and packaging equipments

FOLLOWING CONVENTIONAL TECHNIQUES ARE USED FOR PREPARATION OF FAST DISSOLVING DRUG DELIVERY SYSTEM[32]

Disintegrant Addition

Disintegrant addition technique is one of the popular techniques for formulating Fast-dissolving tablets because of its easy implementation and cost effectiveness. The basic principle involved in formulating Fast-dissolving tablets by disintegrant addition technique is addition of super disintegrants in optimum concentration so as to achieve rapid disintegration along with the good mouth feel.

Freeze Drying

A process in which water is sublimated from the product after freezing. Lyophilization is a pharmaceutical technology, which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water

by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.

Moulding

In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.

Sublimation

The slow dissolution of the compressed tablet containing even highly water soluble ingredients may be due to the low porosity of the tablets. Inert solid ingredients that volatilize readily (e.g. urea, ammonium carbonate, ammonium bicarbonate, hexa methelene tetramine, camphor etc.) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structures. Additionally, several solvents (e.g. cyclohexane, benzene) can be also used as pore forming agents (Figure No.5).

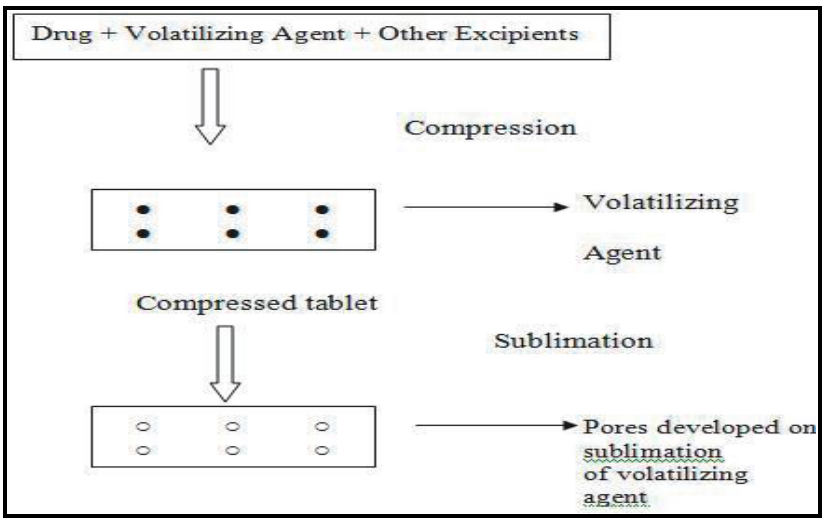


Figure No.5:Sublimation technique for preparation of FDTs

Spray-Drying

Spray drying can produce highly porous and fine powder that dissolve rapidly. The formulations are incorporated by hydrolyzed and non-hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or croscarmellose sodium as disintegrating agent and an acidic material (e.g. citric acid) and / or alkali material (e.g. Sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium.

Mass- Extrusion

- ❖ Particles swell to precompression size and break up the matrix
- ❖ Water is drawn into the pores and particles repel each other due to the resulting electrical force

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product and cut into even segments by using heated blade and to form tablets. The dried cylinder can also be subjected to coat the granules of bitter tasting drugs and thereby masking their bitter taste.

Direct Compression[33]

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can more easily be controlled than that of other production methods. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Disintegrant efficacy is strongly affected by tablet size and hardness, large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration property often have medium to small size and/or high friability

and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all results from insufficient physical strength.

Patented Technologies for Fast Disintegrating Tablets[34]

Each technology has a different mechanism, and each fast-dissolving/ disintegrating dosage form varies regarding the following:

- Mechanical strength of final product
- Drug and dosage form stability
- Mouth feel
- Taste
- Rate of dissolution of drug formulation in saliva
- Swallow ability
- Rate of absorption from the saliva solution and Overall bioavailability

Zydis Technology

Zydis, the best known of the fast-dissolving/disintegrating tablet preparations was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. The Zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth[5].

Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients[6].

Orasolv Technology

Orasolv Technology has been developed by CIMA labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pack and place system[7].

Flash Dose Technology

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat process[28].

Wowtab Technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water ". In this process, combination of low mouldability saccharides and high mouldability saccharides are used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet[29].

Oraquick Technology[35]

The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its microsphere technology, known as MicroMask, has superior mouthfeel over taste-masking alternatives[36]. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more

pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking.There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.

Quick - Dis Technology[37]

Lavipharm Laboratories Inc. (Lavipharm) has invented an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intraoral drug delivery system, trademarked Quick-Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The Quick-Dis™ drug delivery system can be provided in various packaging configurations, ranging from unit-dose pouches to multiple-dose blister packages.

The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for Quick Dis™ film with a thickness of 2 mm. The typical release profile of an active ingredient exhibited by a Quick-Dis™ drug delivery system is 50% released within 30 seconds and 95% within 1 minute.

Nanocrystal Technology[37]

For fast dissolving tablets, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance,

typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary wet milling technique.

NanoCrystal™ Fast dissolving technology provides for:

- Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix
- Product differentiation based upon a combination of proprietary and patent-protected technology elements
- Cost-effective manufacturing processes that utilize conventional, scalable unit operations
- Exceptional durability, enabling use of conventional packaging equipment and formats (i.e., bottles and/or blisters)
- Wide range of doses (up to 200mg of API per unit)
- Use of conventional, compendial inactive components
- Employment of non-moisture sensitive in actives

NanoCrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations (e.g., granulation, blending, and tableting) that generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into ODT dosage forms because manufacturing losses are negligible.

Advantages of FDT

Orodispersable tablets can offer several biopharmaceutical advantages such as improved efficiency over conventional dosage forms. For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules. In addition, FDTs may be suitable for the oral delivery of drugs such as protein and peptide-based

therapeutics that have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. Because drugs delivered in FDTs may be absorbed in the pregastric sites of highly permeable buccal and mucosal tissues of the oral cavity, they may be suitable for delivering relatively low-molecular weight and highly permeable drugs[32-36].

Future possibilities for improvements in FDTs and drug delivery are bright, but the technology is still relatively new. Several drug delivery technologies that can be leveraged on improving drug therapy from MDTs have yet to be fully realized[37, 38].

Table No.3: Some of Promising Drug Candidates for Fast Dissolving Tablets[31]

S.No	Category	Examples
1	Antibacterial agents	Ciprofloxacin, tetracycline, erythromycin, rifampicin, penicillin, doxycyclin, nalidixic acid, trimethoprim, sulphacetamide, sulphadiazine etc.
2	Anthelmintics	Albendazole, mebendazole, thiabendazole, livermectin, praziquantel, pyrantel embonate, dichlorophen etc.
3	Antidepressants	Trimipramine maleate, nortriptyline HCl, trazodone HCl, amoxapine, mianserin HCl.
4	Antidiabetics	Glibenclamide, glipizide, tolbutamide, tolazamide, gliclazide, chlorpropamide etc.
5	Analgesics/anti-inflammatory agents	Diclofenac sodium, ibuprofen, ketoprofen, mefenamic acid, naproxen, oxyphenbutazone, indomethacin, piroxicam, phenylbutazone etc.
6	Antihypertensives:	Amlodipine, carvedilol, diltiazem, felodipine, minoxidil, nifedipine, prazosin HCl, nimodipine, terazosin HCl etc.
7	Antiarrhythmics	Disopyramide, quinidine sulphate, amiodarone HCl, etc.
8	Antihistamines	Acrivastine, cetrizine, cinnarizine, loratadine, fexofenadine, triprolidine etc.

S.No	Category	Examples
9	Anxiolytics, sedatives hypnotics and neuroleptics	Alprazolam, diazepam, clozapine, amylobarbitone, lorazepam, haloperidol, nitrazepam, midazolam, phenobarbitone, thioridazine, oxazepam etc.
10	Diuretics	Acetazolamide, clorthiazide, amiloride, furosemide, spironolactone, bumetanide, ethacrynic acid etc.
11	Gastro-intestinal agents	Cimetidine, ranitidine HCl, famotidine, domperidone, omeprazole, ondansetron HCl, granisetron HCl etc.
12	Corticosteroids	Betamethasone, beclomethasone, hydrocortisone, prednisone, prednisolone, methyl prednisolone etc.
13	Antiprotozoal agents	Metronidazole, tinidazole, omidazole, benznidazole.

Table No.4: Comparison of Fast Dissolving Techniques

S. No	ZYDIS (R.P. SCHERER, INC)		
Novelty		**Handling/Storage**	**Drug release/bioavailability**
1	First to market	Do not push tablet through foil	Dissolves in 2 -10s
2	Freeze Dried	Do not use dosage form from damaged package Sensitive to degradation at humidities > 65%	May allow for pre-gastric absorption leading to enhanced bioavailability
ORASOLV (CIMA LABS, INC)			
1	Unique taste masking	Packaged in patented oil packs	Disintegrates in 5 - 45s depending upon the size of the tablet
2	Lightly compressed		No significant change in drug bioavailability

DURASOLV (CIMA LABS, INC)			
1	Similar to Orasolv, but with better mechanical strength	Packaged in foil or bottles	Disintegrates in 5 - 45s depending upon the size of the tablet
		Package in bottles	No significant change in drug bioavailability
WOWTAB (YAMANOUCHI PHARMA TECHNOLOGIES, INC)			
1	Compressed dosage form	Avoid exposure to moisture or humidity	Disintegrates in 5 - 45s depending upon the size of the tablet
2	Proprietary taste masking	Avoid exposure to moisture or humidity Require specialized Packaging	No significant change in drug bioavailability
FLASHDOSE (FUISZ TECHNOLOGIES, LTD)			
1	Unique spinning mech^{m} producing floss-like crystalline structure as cotton candy	Avoid exposure to moisture and humidity	Dissolves within 1 min Enhanced bioavailability
FLASHTAB (PROGRAPHARM GROUP)			
1	Compressed dosage form containing Drug as microcrystals	—	Dissolves within 1 min

Table No.5: Marketed Fast Disintegrating Tablets[5, 28]

S. No	Name of the Product	Active Ingredients	Company
1	Feldene Fast, Melt	Piroxicam	Pfizer, USA
2	Claritin Reditabs	Loratidine	Schering Plough Corp, USA
3	Mazalit MTL	Rizatritan	Merckasnd Co. USA
4	Zyprexia	Olanzapine	Eli Lilly, USA
5	Nimulid-MD	Nimesulide	Panacea Biotech, India
6	Pepcid RPD	Famotidine	Merck and Co., USA
7	ZopranODT	Ondansetron	Glaxo Wellcome, UK
8	Zooming – ZMT	Zolmitriptan	Astrazeneca, USA
9	Zeplar TM	Selegilline	Amarin Corp, UK
10	Torrox MT	Rofecoxib	Torrent Pharmaceutical, India
11	Romilast	Montelukast	Ranbaxy Labs Ltd. India
12	Mosid-MT	Mosapride citrate	Torrent Pharmaceutical, India

2. LITERATURE REVIEW

Shetal Malke *et.al.,* [39] Carried out the formulation and evaluation of Oxcarbazepine fast dissolve tablets. Fast dissolve tablets of oxcarbazepine were prepared containing avicel pH 102 (microcrystalline cellulose) as a diluent and Ac-Di-Sol (croscarmellose sodium) as a superdisintegrant by wet granulation process. The drug is poorly water-soluble. Hence the drug release was tested in various media and the effect of surfactant on drug release was studied. An effective pleasant tasting and stable formulation containing 12% Ac-Di-Sol, 25% Avicel pH 102 and 8.5 % starch as a binder was found to have a good hardness 4-4.5 kg/cm^2, disintegration time of 28±5 seconds and drug release of not less than 90% within 30 min.

Mishra and Vijaya *et.al.,* [40] Carried out formulation of rapidly disintegrating tablets of Meloxicam using super disintegrants like sodium starch glycolate, Ac-Di-Sol and low molecular weight HPMC. The disintegration time in the oral cavity was tested and was found to be around 1 min. It was concluded that rapidly disintegrating tablets with proper hardness rapidly disintegrates in the oral cavity with enhanced dissolution rate.

Rao *et.al.,* [41] Formulated immediate release tablets of Aceclofenac using different super disintegrants like sodium starch glycolate, starch1500, and Croscarmellose Sodium. The release profile of the drug in the formulation in various dissolution media such as 0.1 N HCl, 0.1 N HCl + 1% SLS (Sodium lauryl Sulphate) and phosphate buffer pH 7 was studied. The formulation containing sodium starch glycolate showed maximum drug release in different dissolution media.

Kuchekar *et.al.,* [42] Formulated and evaluated mouth-dissolving tablets of Levofloxacin. Formulations were designed by factorial design technique. Sodium starch glycolate, Croscarmellose Sodium and treated agar were used as super-disintegrates while microcrystalline cellulose was used as diluent. Direct compression technique was used, as it requires conventional tablet machinery and thus economical process. Formulations containing sodium starch glycolate along with other super-disintegrates, showed rapid *in-vitro and in-vivo* dispersion time, as compared to other formulations.

D.M.Patel*et.al.,*[43]Performed Orodispersible tablets are better choice for the pediatric and geriatric patients. Present study demonstrates the use of factorial design in the formulation of orodispersible tablets of Rofecoxib. Preliminary screening of three superdisintegrants namely sodium starch glycolate, crospovidone and Croscarmellose Sodium was carried out (batches AA1 to AA9) and crospovidone was found most effective giving lowest disintegration time and wetting time. Batches AA10 to AA12 were prepared to optimize the amount of crospovidone and the optimum concentration of crospovidone was found to be around 10%. From the preliminary results, a 3^2 full factorial design was employed for preparation of tablets possessing optimized characteristics (batches AA 13 to AA 21). The percentage of crospovidone (X_1) and mannitol (X_2) were selected as independent variables. Wetting time and disintegration time were selected as dependent variables (response; Y). Full and refined models were derived for the prediction of the response variable Y. Based on the results of multiple linear regression analysis, it was concluded that lower disintegration time and wetting time could be obtained when X_1 is kept at high level and X_2 is kept at low level. Promising batch (batch AA 18) was compared with two marketed samples (brand A and B) of rofecoxib tablets for in vitro drug release after 30 min in three dissolution media. Tablets of batch AA 18 exhibited better drug dissolution after 30 min than the tablets of brand A and B in all the dissolution media.

Yu-Chih Shen *et.al.,*[44].Studied orally disintegrating Olanzapine for the treatment of a manic patient with esophageal stricture plus chronic pharyngitis. The case report shows that ODT(orodispersible tablet) olanzapine may be useful in the psychiatric management of manic and other patients for whom have an underlying medical condition they impedes swallowing oral medications.

Mishra *et.al.,*[45]Formulated rapidly disintegrating oral tablet of valdecoxib using superdisitegrants following direct compression technique. It was concluded the fast disintegrating /dissolving tablet of the poorly soluble drug can be made by direct compression technique using selective superdisitegrants showing enhanced dissolution (i.e. improved bioavailability) and hence better patient compliance and effective therapy.

Shishu *et.al.,* [46] Prepared tablets rapidly disintegrating in saliva containing bitter taste masked granules by compression method. The taste masked granules of Chlorpheniramine were prepared using aminoalkyl methacrylate copolymers (Eudragit E-100) by the extrution method. These taste masked granules were directly compressed into tablets using sodium starch glycolate as a superdisintegrant and evaluated for taste by both spectrophotometric method and through panel testing.

Amin *et.al.,* [47]Formulated and evaluated Ofloxacin, a second-generation fluoroquinolone, is a bitter antibacterial. Taste masked adsorbates of ofloxacin were prepared using cationic exchange resins. Metronidazole benzoate, a less bitter salt of Metronidazole along with the taste-masked complex of Ofloxacin, was incorporated into palatable melt in mouth tablets, which are patient compliant. Taste evaluation of the tablets showed complete masking of the bitterness of Ofloxacin. Use of ion exchange resin as superdisintegrants was explored in melt in mouth tablets and a comparative study with existing superdisintegrants was carried out. The tablets were evaluated for various quality control parameters and they exhibited optimum physicochemical characteristics. *In-vitro* release studies revealed complete drug elution from the complex at pH 1.2.

Pandey *et.al.,* [48]Carried out formulation and evaluation of Chloroquine phosphatetablets using three superdisintegrants,sodium starch glycolate, croscarmellose, crospovidone. The performance of three superdisintegrants was found out using intragranular and extragranular methods, both in the same quantity of 2% w/w. The study concluded that intragranular method of incorporation of disintegrants was better than extargranular method and Croscarmellose Sodium incorporated intragranular method gave better result than extragranular method.

Lalla *et.al.,* [49]Prepared fast dissolving Rofecoxib tablets using Nymcel ZSX, Hyswell and Kollidon CL by two techniques viz. wet granulation with starch paste and direct compression. Both the formulations showed complete release of drug within 12 minutes.

Yyoshiteru watanabe *et.al.,* [50]Prepared rapidly disintegration tablet in saliva in the mouth by direct compression using microcrystalline cellulose, low-substituted

hydroxyl propyl cellulose showed rapid disintegration within 30 seconds was obtained in vitro using compounding ratios of microcrystalline cellulose to low-substituted hydroxy propyl cellulose.

Akihiko *et.al*.,[51] Developed an oral dosage form for elderly patients by using agar as base of rapidly disintegration oral tablets. The rapid disintegration of the treated agar tablets seemed due to be rapid water penetration into the tablet resulting from the large pore size and large overall pore volume. It was found that rapidly disintegrating oral tablets with proper hardness could be prepared using treated agar.

Shirwaikar*et.al.,*[52] Formulated Atenolol fast disintegrating tablet using three superdisintegrants croscarmellose sodium, crospovidone, and sodium starch glycolate by dry granulation method. Croscarmellose Sodium proved to be the best among the three and showed satisfactory results.

Toshihiro Shimizu *et.al.,*[53]Carried out formulation study for Lansoprazole fast dissolving tablet containing enteric coated micro granules in which they studied effect of compression on dissolution behaviour.

Mukesh Gohel *et.al*.,[54]Formulated mouth dissolving tablet of Nimesulide. Granules containing Nimesulide, camphor, crospovidone and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by exposure to vacuum. The porous granules were then compressed and evaluated. The result for obtaining a rapidly disintegrating dosage forms tablets should be prepared using an optimum concentration of camphor and a higher percentage of crospovidone.

Mahajan *et.al,*.[55]Carried out formulation of mouth dissolving tablets of Sumatriptan succinate using super disintegrants like sodium starch glycolate,carboxy methylcellulose sodium, and treated agar by direct compression method. Almost 90% of drug was released from all formulation within 10 minutes. The formulation containing combination of sodium starch glycolate and carboxy methylcellulose was found to give the best results.

Aithal*et.al*.,[56]Carried out formulation of fast dissolving tablets of Granisetron Hydrochloride using superdisintegrants by employing direct compression method.

Formulation containing crospovidone and Croscarmellose Sodium displayed shortest disintegration time compare to other disintegrants.

Chaudhari *et.al.,* [57]Carried out formulation and evaluation of fast dissolving tablets of Famotidine by using different superdisintegrants (Ac-Di-Sol and Polyplasdone) with varying concentrations (2%, 3%, 4%, 5%). The bitter taste of Famotidine was masked using drug and eudragit E-100 in different ratios (1:1 – 1:10). The dissolution release rate was found to be 100% on four minutes.

Devi *et.al.,* [58]Carried out formulation of orodispersible tablets of Fluconazole using two different volatilizable compounds viz. ammonium chloride and camphor by wet granulation method. Best formulation were chosen and compared with marketed conventional tablets. No significant difference between the technological properties of the prepared formulation and the marketed tablets.

Sreenivas *et.al.,* [59]Carried out formulation and evaluation of mouth disintegrating tablets of ondansetron hydrochloride by direct compression method, by using disintegrants like crospovidone, Croscarmellose Sodium, pregelatinised starch, sodium starch glycolate that 10% disintegrate concentration was suitable for the preparation of ondansetron hydrochloride tablets containing disintegrant crospovidone and Croscarmellose Sodium were the best.

Jinichi Fukami *et.al.,* [60]Formulated fast disitegrating compressed tablets using amino acid such as L-lysine HCl, L-alanine, Glycine, and L-tyrosine as disintegration accelerator. The tablet having hardness of about 4 kg/cm^2. The wetting time of the tablets increased in the order of L-lysine HCl. L-alanine, glycine and L-tyrosine. Whereas disintegration time in the oral cavity of the tablets increased in the order of L-alanine, glycine, L-lysine HCl, and L-tyrosine. When the polar component was small value, faster wetting of tablet was observed. When the dispersion component was small value, faster disintegration of tablet was observed except of L-tyrosine tablet.

Fabio Baldi*et.al.,* [61]Carried out the studies on lansoprazole fast disintegrating tablet: A new formulation for an established proton pump inhibitor. Lansoprazole is a proton

pump inhibitor, which is an effective and well-tolerated treatment option in the management of acid related disorders. Lansoprazole fast disintegrating tablet (LFDT)- a new, patient friendly and more convenient formulation of lansoprazole, which can be taken with or without water, is the first PPI to be made available as an orally disintegrating tablet. Studies have shown that the bioavailability of LFDT is comparable to lansoprazole capsules, at both 15 and 13 mg doses, the indications and recommended dosages for LFDT are therefore identical to lansoprazole capsules. The new formulation may be of particular benefit to those with active life styles who do not always have water available, patients who have difficulty in swallowing and elderly patients.

Saini *et.al.,* [62]Carried out the formulation of lamotrigine oro-dispersible tablets by superdisintegrating agents. Lamotrigine oro-dispersible tablets were formulated by using combination of low substituted hydroxypropylcellulose (10% w/w) and crospovidone (6% w/w) as superdisintegrating agents. Direct compression method was employed for the preparation of lamotrigine oro-dispersible tablets. The developed lamotrigine oro-dispersible tablets showed good taste and excellent feel and rapid dispersion in mouth.

Na Zhao *et.al.,* [63]Studied functionally comparison of three classes of super disintegrants in promoting aspirin tablet disintegration and dissolution. The aim of the study was to compare the disintegration efficiency, and to develop a discriminating test model for the three classes of super disintegrants represented by Ac-Di-Sol, primojel, and polyplasdone. Using a digital video camera to examine the disintegration process of tablets containing the same w/w percent concentration of the disintegrants, Ac-Di-Sol was found to disintegrate tablets rapidly into apparently primary particles, primojel also apparently disintegrated tablets into primary particles but more slowly, polyplasdone XL10 disintegrated tablets rapidly but into larger aggregated particles. The differences in the size distribution generated in the disintegrated tablets likely contribute to the drug dissolution rate differences found in aspirin tablets with similar disintegration rates.

Amrutkar *et.al.,* [64]Carriedout comparative evaluation of disintegrants by formulating Famotidine dispersible tablets by using various disintegrants like Croscarmellose Sodium, crospovidone, indion 414 and sodium starch glycolate was prepared with a view to increase its solubility. Among the four disintegrants added, the tablets prepared with Croscarmellose Sodium were superior with respect to disintegration and dissolution characteristics.

Vikesh Shukla *et.a.l.,* [65]Carried out the formulation and evaluation of piroxicam dispersible tablets using natural disintegrants. The tablets of piroxicam was prepared by direct compression and wet granulation methods using starch paste as binder and superdisintegrants like isapgol husk, tragacanth, cassia tora. The dispersible tablet formulated using cross-linked tragacanth showed highest dissolution rate. Kinetic studies indicates that all the formulations followed first order release kinetics with diffusion mechanism.

Chowdhary *et.al.,* [66].Carried out effect of primogel and surfactants on the dissolution of piroxicam from capsule formulations. Piroxicam was formulated into capsules with primogel, tween 80, and SLS. The capsules were evaluated for drug content, disintegration and dissolution rate. The order of efficiency of these materials in increasing dissolution of piroxicam was found to be tween 80>SLS >primogel. They concluded as primogel and surfactants were found to increase the dissolution of piroxicam from capsule formulations.

Basak *et.al.,* [67]Carried out studies in formulation of Ampicillin dispersible tablets. Ampicillin dispersible tablets were formulated employing superdisintegrating agents like sodium starchglycolate,microcrystalline cellulose and starch.The tablets were prepared by wet granulation method.The tablets containing more quantity of sodium stachglycolate exhibited quick disintegration followed by tablets containg microcrystalline cellulose in a disintegrating mixture of sodiumstarchglycolate, microcrystalline cellulose and starch.It can be concluded that tablet prepared with sodium starch glycolate,micro crystalline cellulose, starch in ratios 20mg:10mg:10mg per tablet with ethycellulose as granulating agent is promising for ampiciilin dispersible tablet.

Santanu Chakraborthy*et.al.,*[68]Studied the comparative study on effect of natural and synthetic superdisintegrants in the formulation of fast dissolving tablets.In the present study,the effect of natural superdisintegrants like isolated mucilage of plantago ovata and synthetic superdisintegrants like sodium starch glycolate and croscarmellose sodim were compared in the formulations of fast disintegrating tablets prepared by direct compression method using microcrystalline cellulose as direct compressible vehicle.Tablets were evaluated for weight variation, hardnees,disintegration test,drug content,friability,dissolution,swelling index.They are concluded that among all superdisintegrants,plantago ovata mucilage showed the highest swelling index and better disintegrating property than synthetic superdisintegrants.

Raghavan *et.a.l.,*[69] Studied the effect of Aspirin on pharmacokinetics of piroxicam in healthy male volunters. The influence of aspirin on the pharmacokinetics and pharmacodynamics of piroxicam is not known. The study indicates that pharmacokinetic parameters $C_{max}$and T_{max} are not altered on concurrent administration of aspirin.

Ramarao*et.al.,*[70]Carried out the improvement of dissolution rate and bioavailability of piroxicam with pregelatinizwd starch. Piroxicam dispersions in pregelatinized starch (PGS) were prepared in different drug and carrier ratios and were characterized byX-raydiffractograms (XRD), differential scanningcalorimetry (DSC). They observed that all the tablets formulated with piroxicam pregelatinized starch physical mixtures, dispersions were found to contain piroxicam within 100±5% of the labelled claim. Finally concluded that fast disintegrating tablets giving rapid dissolution of the drug could be formulated employing piroxicam pregelatinized starch dispersions by conventional wet granulation method.

3. AIM AND OBJECTIVE

Need of the present work

For the past two decades, there has been enhanced demand for more patient compliance dosage forms. As a result, the demand for their technologies has been increasing three fold annually. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with dosing frequency to minimize side effects.

- This results in slower dissolution and absorption rates on oral administration and is one of the causes of gastro intestinal side effects
- Improvement in drug solubility expected to enhance its bioavailability and reduce local side effects

Difficulty in swallowing (dysphasia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with these groups. Other categories also several problems in using conventional oral dosage forms include the mentally ill, uncooperative patients suffering from nausea, sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to nonavailability of water. These problems led to the development of levofloxacin as mouth dissolving tablets. Which disintegrate and dissolve in saliva without the need of drinking water. The saliva serves to rapidly disperse the dosage form and the dissolved medicament is swallowed along with saliva in normal way. As the dissolved medicaments along with saliva passes down into stomach, they are absorbed from the mouth, pharynx, and oesophagus. Therefore the bioavailability of levofloxacin is significantly greater than those observed from conventional levofloxacin dosage forms.

4. PLAN OF WORK

Levofloxacin is an antibiotic used for treatment of a number of infections including infection of joints and bones, gastroenteritis, malignant otitis externa, respiratory tract infections, cellulities, urinary tract infections, anthrax, skin structural infections, typhoid fever and it also used in treatment of community acquired pneumonia, chronic bacterial prostitis, nosocomial pneumonia etc.

- ❖ It has prolonged half-life about 8 hrs
- ❖ It is poorly water soluble drug
- ❖ When a poorly water soluble drug administered orally it may cause problems in bioavailability and dissolution rates due to its poor solubility in biological fliuds
- ❖ Hence the present work was aimed at increasing the rate of dissolution of Levofloxacin thus providing faster rate of absorption by adding potential superdisintegrants like croscarmellose sodium, crospovidone, and sodium starch glycolate in different concentrations
- ❖ To mask the bitter taste of Levofloxacin, Saccharin sodium was used as sweetening agent
- ❖ Seven formulations of orodispersible tablets of Levofloxacin were prepared using three different super disintegrants namely croscarmellose sodium, crospovidoneand sodium starch glycolate with three concentrations prepared by direct compression method
- ❖ The prepared Levofloxacin orodispersible tablets using different concentrations were evaluated by *invitro* drug release studies

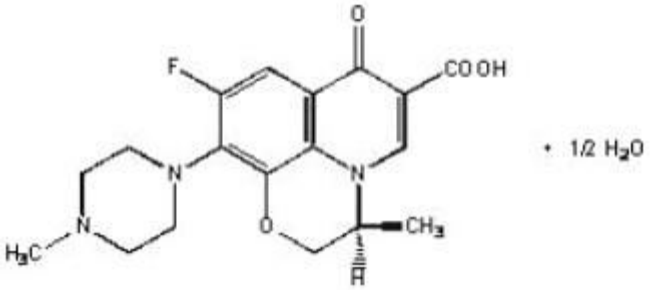
The study was planned to carry out as follows:

Preparation of seven formulations of orodispersible tablets of Levofloxacinby using different superdisintegrants in three different concentrations.

1. Evaluation study of powder mixed blend of drug and excipients:
    - Angle of repose
    - Bulk density
    - Tapped density
    - Compressibility index
    - Hausner ratio
2. Drug and excipients interaction studies by FTIR.
3. Compression of tablets by "Direct Compression method".
4. Evaluation of tablets:
    - Weight variation
    - Hardness
    - Thickness
    - Friability
    - Disintegration time
    - Estimation of drug content
    - Water absorption test.
5. *In-vitro* drug release studies.
6. Stability studies

5. DRUG PROFILE

LEVOFLOXACIN[71]



CHEMICAL DATA

Chemical name	:	(-)-(s)-9_fluoro 2,3-dihydro 3-methyl 10 (4-methyl-1-Piperazinyl 7-oxo- 7 Pyridol (1, 2, 3 De)-1,4 Benzoxazine 6- carboxylic acid hemihydrate
Formula	:	C_{18} H_2O F N_3O_4 .½ H_2O
Molecular mass	:	331.37 g/mol

PHYSICAL DATA

Solubility	:	Freely soluble at pH range of 0.6 to 5.8 and it shows Maximum solubility at pH 6.7
Melting point	:	214-216° C
Drug Category	:	Fluoroquinolones

PHARMACOKINETIC DATA

Absorption	:	Rapidly and well absorbed from GIT with peak plasma Concentration
Bioavailability	:	99%
Half life	:	6-8 hours
Distribution	:	Bile (high concentration) ,CSF(10%) ,crosses placental barrier

Protein binding	:	24-38%
Metabolism	:	Hepatic including CYP A2
Excretion	:	Renal (major), non renal routes like hepatic, billiary, transluminal Secretion

Mechanism of Action[72]

Levofloxacin Hcl drug has *invitro* activity against a wide range of Gram negative and Gram positive organism. Levofloxacin inhibits bacterial DNA gyrase, an enzyme responsible for countering excessive supercoiling of DNA during replication of transcription. Levofloxacin also inhibits a type 2 topoisomerase and isomerise which leadsto inhibition of cell division in infective microorganism.

Uses[73]

Levofloxacin is used for treatment of a number of infections including infection of joints and bones, gastroenteritis, malignant otitis externa, respiratory tract infections, cellulities, urinary tract infections, anthrax, skin structural infections, typhoid fever and italso used in treatment of community acquired pneumonia, chronic bacterial prostitis,nosocomial pneumonia etc.

Brand Names - Levaquin, Adlox, Aflevo etc

Available Dosages - Tablets, Intravenous and ophthalmic solutions

Dosing - Adult dose is 250-750mg (immediate release tablets) for Every 12hours or 500-1000mg (extended release tablets), 200-400mg (i.v), Child dose is 250 mg/kg bid.

Contraindications

Levaquin administration may become contraindicated in some patientswith a history of hypersensitivity to Levofloxacin and it also contraindicated in patients withepilepsy and other seizure disorders.

Pregnancy

Levofloxacin comes under pregnancy category C where there is no evidencestudies of Levofloxacin in pregnant women so it should not used during pregnancy.

Nursing Mothers

Levofloxacin should avoid in nursing women.

Pedriatic population

Levofloxacin should not used in infants as they have not developedsufficient enzymes to metabolise drug and it should not used to children via intravenous route.

Adverse reactions[74]

Levofloxacin may cause mild adverse reactions like nausea, vomiting,diarrhoea,rashes, abnormal liver functions and it may cause some rare but serious adverse effects like Myasthenia gravis including muscle weakness, breathing problem,neuropathy,photosensitivity reactions etc.

Drug Interaction

Levofloxacin may interact with some drugs as well as a herbal and natural supplements. Levofloxacin also interacts with NSAIDS causes Black box warning which leads to Achiles tendon rupture.It also interact with theophylline and this interaction may increases the risk of cardiotoxicity, arrhythmias and anticoagulation.

Storage

Oral products should be stored at 5-25^{0}C, Ophthalmic products should be stored At 2-25 C intravenous solutions should be stored at 25^{0}C.

6. A GENERAL PROFILE ONSUPER DISINTEGRANTS AND EXCIPIENTS USED IN THE STUDY

Bioavailability of a drug depends upon the absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. Use of super disintegrants is the basic approach in development of fast disintegration tablets. Super disintegrants play a major role in the disintegration and dissolution of ODT. It is essential to choose a suitable super disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. Superdisintegrants provide quick disintegration due to combined effect of swelling and water absorption.Due to swelling of superdisintegrants, the wetted surface of the tablet increases and thus promotes disintegration and dissolution the drug in the formulation[75].

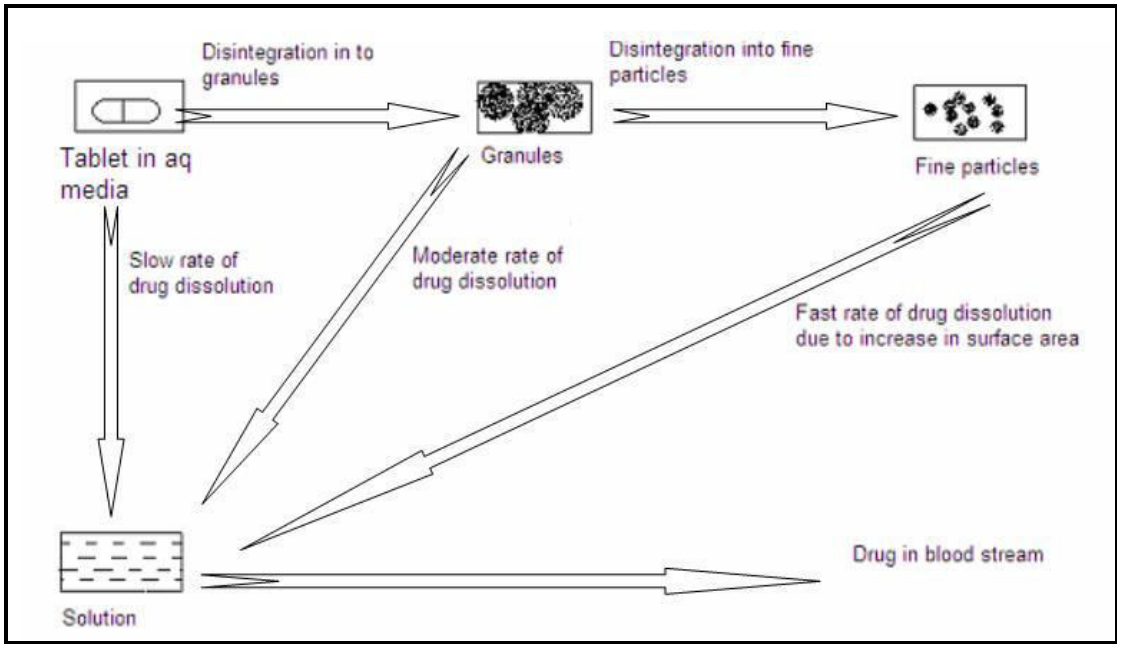


Figure No.6: Tablet disintegration and subsequent drug dissolution

SODIUM STARCH GLYCOLATE

General description[76]

Nonproprietary Names

BP : Sodium starch glycollate

USP NF : Sodium starch glycolate

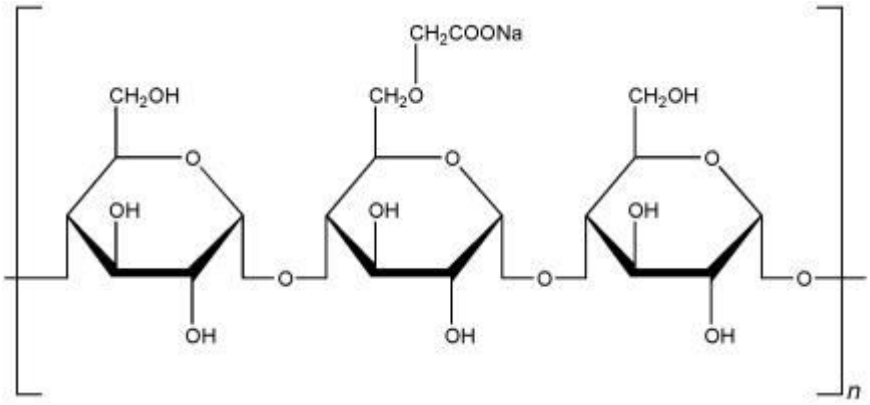
Synonyms

Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel; starch Carboxymethyl ether, sodium salt; Tablo.

Chemical Name

Sodium carboxymethyl starch

Structural Formula



Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology[77]

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum

concentration about 4%, although in many cases 2% is sufficient.Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time.Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description[78]

Sodium starch glycolate is a very fine, white or off white,free flowing powder, odourless.

Typical Properties

Alkalinity	:	pH 3-5 % or pH =5.5-7.5 %. For a 3.3% aqueous dispersion.
Density (bulk)	:	0.756 g/cm^3
Density(tapped)	:	0.945 g/cm^3

Solubility

Sparingly soluble in ethanol (95%), practically insoluble in water.

Stability and Storage Conditions

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.The physical properties of sodium starch glycolate remain unchanged for up to 3-5 years if it is stored at moderate temperatures and humidity.

Safety

Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

CROSPOVIDONE

GENERAL DESCRIPTION[78]

Nonproprietary Names

BP : Crospovidone

USP NF : Crospovidone

Synonyms

Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name

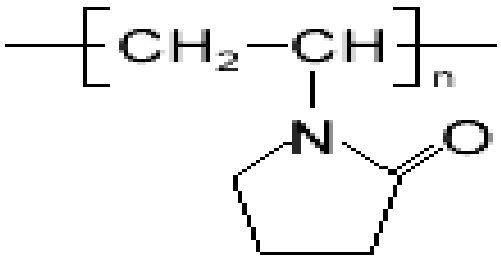
1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula $(C_6H_9NO)_n$

Molecular Weight1,000,000

The USPNF 23 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of N-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

Structural Formula



Functional Category

Tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology[79]

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2-5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Typical Properties

Acidity or Alkalinity	:	pH =5.0-8.0. %(1% w/v aqueous slurry)
Density (bulk)	:	0. 363 g/cm^3
Density (tapped)	:	0. 543 g/cm^3

Solubility

Practically insoluble in water and most common organic solvents.

Stability and Storage Conditions[79]

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.

CROSCARMELLOSE SODIUM

General Description[76]

Nonproprietary Names

BP : Croscarmellose Sodium

USP NF : Croscarmellose Sodium

Synonyms

Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

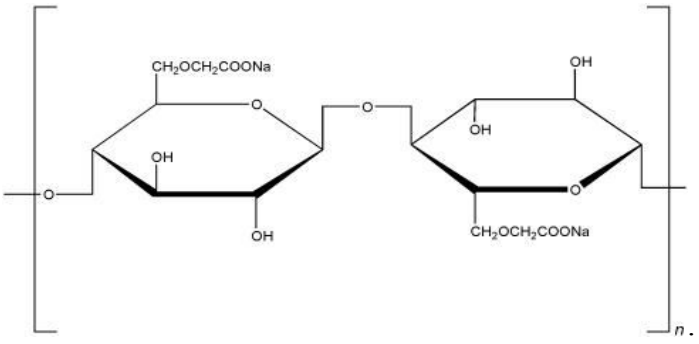
Chemical Name

Cellulose, carboxymethyl ether, sodium salt.

Empirical Formula and Molecular Weight

Croscarmellose Sodium is a crosslinked polymer of carboxymethylcellulose sodium. The USP 28 describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose. Typical molecular weight is 90 000-700 000.

Structural Formula



Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology[80]

Croscarmellose Sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules.In tablet formulations, Croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the Croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.Croscarmellose Sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Description

Croscarmellose Sodium occurs as an odorless, white or grayish-white powder.

Typical Properties

Acidity or Alkalinity	:	pH =5.0-7.0 % (1% w/v solution in Co_2 free water)
Density (bulk)	:	0. 529 g/cm^3
Density (tapped)	:	0. 819 g/cm^3

Solubility

Practically insoluble in water. Although, swells rapidly 4-8 times its original volume on contact with water.

Stability and Storage Conditions[81]

Croscarmellose sodium is a stable through hygroscopic material.A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months.Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

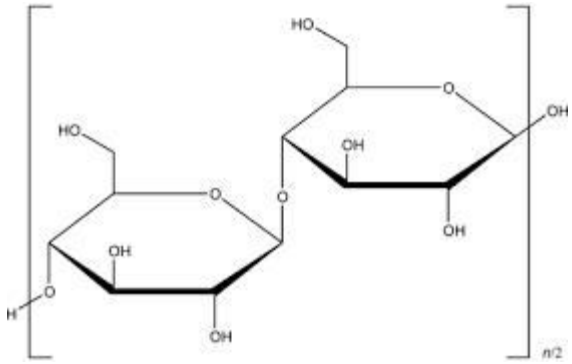
Safety

Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems.

In the UK, croscarmellose sodium is accepted for use in dietary supplements. The WHO has not specified an acceptable daily intake for the related substance carboxy methyl cellulose sodium, used as a food additive, since the levels necessary to achieve a desired effect were not considered sufficient to be a hazard to health.

MICROCRYSTALLINE CELLULOSE

Structural formula



GENERAL DESCRIPTION[76]

Nonproprietary Name

Microcrystalline cellulose

Synonym

Avicel

Empirical formula

$(C_6 H_{10} O_5)_n$

Molecular weight

36,000

Specific surface area

1.21-1.30 m^2/g

Nominal mean particle size

100 μm

Pharmaceutical applications[82]

Avicel is widely used in pharmaceuticals, primarily as a binder or diluent in oral tablet and capsule formulation where it is used both in wet granulation as well as direct compression processes. In addition to its use as a binder or diluent it also has a disintegrant and lubricant property that makes it useful in tabletting.

Pharmaceutical applications of Avicel

Use	Concentration (%)
Adsorbent	20 – 90
Anti-adherent	5 – 20
Capsule diluent	20 – 90
Tablet disintegrants	5 – 15
Tablet binder/ Diluent	20 – 90

Description

Avicel is purified, partially depolymerised cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades, which have different properties and applications.

Typical Properties

Acidity or Alkalinity : 5-7.5
Density(bulk) : 0.337 g/cm ^{3}
Density (tapped) : 0. 478 g/cm ^{3}
Melting Point : Chars at 260^0C – 270^0C

Solubility

practically insoluble in water, dilute acids and most organic solvents. Slightly soluble in 5%w/v sodium hydroxide solution.

Functional Category

Adsorbent, tablet and capsule diluent, tablet disintegrant.

Stability and storage conditions[83]

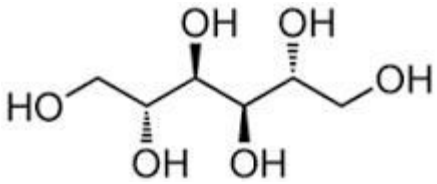
Avicel is a stable though hygroscopic material. The bulk material should be stored in a well closed container in a cool, dry place.

Safety

It is generally regarded as a nontoxic and nonirritant material. It is not absorbed systemically and thus has little toxic potential. Deliberate abuse of formulations containing cellulose as inhalation has resulted in formation of cellulose granulomas.

MANNITOL

Structural formula



GENERAL DESCRIPTION[78]

Empirical formula

$C_6H_{14}O_6$

Molecular weight

182.17

Melting point

166-168^{0}C

Functional category

Sweetening agent, tablet and capsule diluent, tonicity agent, vehicle (vehicle agent) for lyophilized preparation.

Applications in Pharmaceutical Formulation or Technology[84]

In Pharmaceutical preparation, it is primarily used as diluent (10-90%) in tablet formulations.

Description

Mannitol occurs as white, odorless, crystalline powder, or free flowing granules. It has sweet taste, approximately sweet as glucose.

Typical Properties

Density (bulk)	:	0. 430 g/cm ^{3}
Density (tapped)	:	0. 734g/cm ^{3}

Solubility

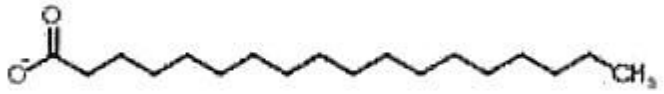
In alkalis it is soluble. In water sparingly soluble.

Stability and Storage Conditions[85]

Mannitol is stable in the dry state and in aqueous solutions. The bulk material should be stored in a well closed container in a cool, dry place.

MAGNESIUM STEARATE

Structural formula



GENERAL DESCRIPTION[78]

Nonproprietary Names

BP : Magnesium stearate

USP NF : Magnesium stearate.

Synonyms

Hyqual, magnesium octadecanoate stearic acid magnesium salt.

Chemical Name

Octadecanoic acid magnesium salt.

Empirical Formula

$C_{36}H_{70}$ MgO4.

Molecular weight

591.27.

Functional category

Tablet and capsule lubricant.

Moisture content

3.85%.

Application in pharmaceutical formulation or technology

Magnesium stearate is widely used in cosmetics, food and pharmaceutical formulations. It is primarily used as lubricant in capsule and tablet manufacture at concentrations between 0.2-5.0 percent.

Description

Magnesium stearate is a fine, white, precipitated or milled, impalatable powder of low bulk density having a faint, characteristic odour and taste, the powder is greasy to touch and readily adheres to the skin.

Typical properties

Flowability	:	Poorly flowing, cohesive powder
Density(bulk)	:	0.159g/cm^3
Density(tapped)	:	0. 286g/cm^3
Melting point	:	88.5^{0}C

Solubility

Practically insoluble in ethanol, ethanol 95%, ether and water: slightly soluble in warm benzene and warm ethanol 95%.

Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well – closed container in a cool and dry place.

Safety[86]

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation. Inhalation of magnesium stearate powder is harmful and has resulted in fatalities.

7. MATERIALS AND METHODS

PRE FORMULATION STUDIES

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

STANDARD CURVE OFLEVOFLOXACIN

Potassium dihydrogen phosphate solution, 0.2M[87]

27.218gm of potassium dihydrogen phosphate was dissolved in 1000ml distilled water in a volumetric flask.

Sodium hydroxide solution, 0.2M

8gm of sodium hydroxide was dissolved in 1000ml distilled water and it gives 0.2M solution.

Preparation of pH 6.8 buffer

Place 50.0ml of 0.2M potassium dihydrogen phosphate in a 200ml volumetric flask add 22.4ml of 0.2M sodium hydroxide and then make up with water upto volume.

Preparation of levofloxacin stock solution

100 mg of pure drug of Levofloxacin was dissolved in 100ml volumetric flask. The drug was shaked with 5ml methanol. For the above solution, add remaining amount was make up with 6.8pH Phosphate buffer. This solution contains 1000µg/ml of levofloxacin stock solution. Take 10ml from above solution in 100ml volumetric flask and make up with 6.8pH Phosphate buffer. This solution contains 100µg/ml of drug. From above solution take 1 ml in 10ml volumetric flask and make up with 6.8 pH Phosphate buffer. From this solution pipette out 0.2 ml in 10ml volumetric flask add buffer. This gives 0.2µg/ml Solution. Similarly, preparing the 0.4ml, 0.6ml, 0.8ml and 1ml of solutions in 10ml volumetric flasks Resulting gives, 2µg/ml, 4µg/ml,

6µg/ml, 8µg/ml and 10µg/ml solutions. The concentrated solution scanned in UV-Visible Spectrophotometer with absorption maximum is 298nm.

STANDARD CURVE OF LEVOFLOXACIN

Table No.6: Standard curve of Levofloxacin in Phosphate buffer (pH 6.8)

S.No	Concentration (µg/ml)	Absorbance (298nm)
1	0	0.00
2	2	0.232
3	4	0.465
4	6	0.684
5	8	0.926
6	10	1.126

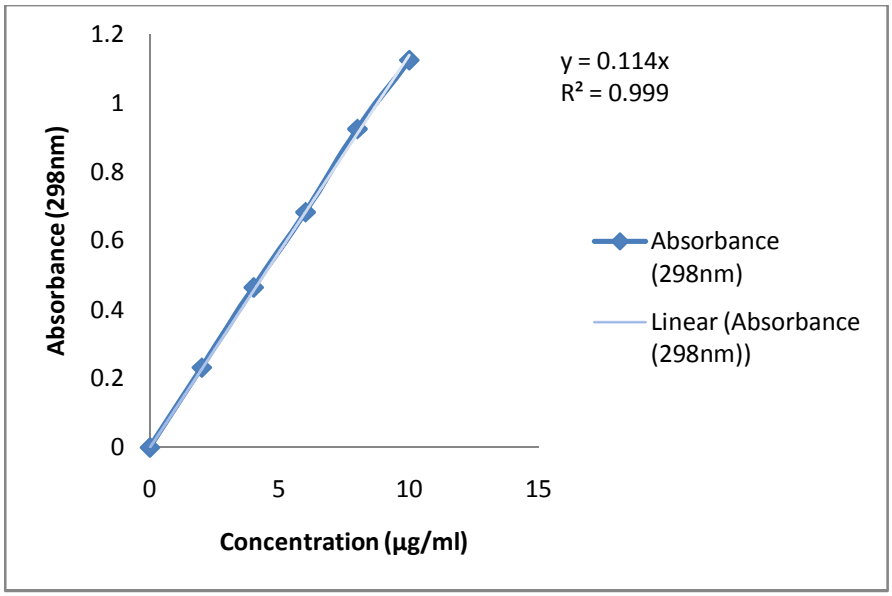


Figure No.7: Standard curve of Levofloxacin in Phosphate buffer (pH 6.8)

METHOD OF PREPARATION

PREPARATION OF LEVOFLOXACIN TABLETS:

Direct Compression Technique:

This method is used when the ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be pre-processed. This requires the active ingredient to have appropriate physical and chemical properties, such as good compatibility and low stickiness. Direct compression is often preferred because of its simplicity and relatively low cost, but may not always be technically feasible.

In this method, all the powder excipients are mixed thoroughly in a polyethylene bag. After proper mixing, the powder was punched into tablets. The weight of the tablet was 400mg and dose of the drug is 150mg[88].

Table No.7: Different Formulation of Levofloxacin Oral Dispersible Tablets

S. No	Formulation Code	Drug mg	SSG mg	CCS mg	CP mg	Avicel PH102 mg	Mannitol mg	Sodium Saccharin mg	Magnesium Stearate mg	Mint flavor mg
1	FLOT-1	150	90	-	-	100	45	10	5	q.s
2	FLOT-2	150	-	90	-	100	45	10	5	q.s
3	FLOT-3	150	-	-	90	100	45	10	5	q.s
4	FLOT-4	150	45	45	-	100	45	10	5	q.s
5	FLOT-5	150	-	45	45	100	45	10	5	q.s
6	FLOT-6	150	45	-	45	100	45	10	5	q.s
7	FLOT-7	150	30	30	30	100	45	10	5	q.s

Each Tablet wt – 400mg.

EVALUATION PARAMETERS

PRECOMPRESSION STUDIES OF POWDER BLENDS

Bulk density[89]

Bulk density is the ratio between a given mass of powder or granules and its bulk volume. Accurately weighed quantity of granules was carefully transferred into 100ml measuring cylinder, initial volume was measured and calculated according to the formula

Bulk density = Mass / Volume

Tapped density

Tapped density is the ratio between a given mass of powder or granules and the constant or fixed volume of the powder or granules after tapping. Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed.

Tapped density = Weight of granules/ Tapped volume of granules

Angle of Repose[90]

Angle of repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. The angle of repose of the power or granules was determined by fixed funnel method to assess the flow property of the powder or granules. The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods(Table No.8). The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and

measure the included angle with the horizontal. The angle of repose (**θ**) was calculated by using the following formula:

$$\theta = \mathrm{Tan}^{-1}(h/r)$$

Where,

θ = **Angle of repose,**

h = Height of the powder cone,

r = Radius of the powder cone.

Table No.8: Angle of Repose I.P limits

S.No	Angle of Repose	Powder flow
1	< 25	Excellent
2	25 – 30	Good
3	30 – 40	Passable
4	> 40	Very poor

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density (Table No.9).

The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where, TD = Tapped density

BD = Bulk density

Table No.9: Carr's Index I.P limits

S.No	Carr's Index	I.P Limits value
1	Excellent	<10
2	Good	11 – 15
3	Fair	16 – 20
4	Possible	21 – 25
5	Poor	26 – 31
6	Very poor	32 – 37
7	Very very poor	>38

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules (Table No.10).The hausner's ratio was calculated by using the following formula.

Hausner's Ratio = Tapped density/Bulk density

Table No.10: Hausner's RatioI.P Limits

S. No	Hausner's Ratio	I.P Limits value
1	Excellent	1.00 – 1.11
2	Good	1.1 – 1.18
3	Fair	1.19 – 1.25
4	Possible	1.26 -1.34
5	Very poor	1.35 -1.45
6	Very very poor	>1.60

POSTCOMPRESSION STUDIES OF LEVOFLOXACIN TABLETS

To design tablets and later to monitor tablets production, and quality, quantitative evaluation, assessments of tablets physical, chemical, and bioavailability properties must be made.

There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, thickness, weight variation, hardness, disintegration and dissolution characters. The diameters and shape depends on the die and punches selected for the compression of tablets. The remaining specifications assure that tablets do not vary from one production lot to another. The following standards or quality control tests should be carried out on compressed tablets:

Hardness or Crushing strength Test[91]

Hardness is a force required to break a tablet across a diameter. Hardness of the tablet was determined using the Monsanto hardness tester (The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10kg ; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10 -20 kg)[11].

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Vernier calliper and the reading was recorded in millimeters.

Friability Test[92]

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. It is usually measured by the use of the Roche friabilator. The pre-weighed tablets were placed in the friabilator which was then operated for 100rpm, then dusted and reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable. The percent friability was determined using the following formula.

$$\text{Friability} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Where,

W_1 = Weight of ten tablets before test

W_2 = Weight of ten tablets after test

Weight variation test

This is an important in-process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablet (for any reason) leads to either under medication or overdose. Therefore, every tablet in each batch should have a uniform weight. Twenty tablets of each formulation were selected at random and weighed individually. The weight of individual tablets was noted. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. Not more than two of the tablets must differ from the average weight by not more than the percentages stated in table below. The percentage deviation was calculated by using the following formula.

$$\text{Percentage Deviation} = \frac{\text{Individual weight - Average weight}}{\text{Average weight}} \times 100$$

Table No.11: Weight variation Tolerances for uncoated Tablets

S. No	Average weight of Tablets(mg)	Maximum % difference allowed
1	130 or less	± 10
2	130-324	±7.5
3	More than 324	±5

Estimation of Drug Content[93]

The term "Uniformity of dosage unit" is defined as the degree of uniformity for substance among dosage units. The test for content uniformity is based on the assay of the active medicament of content uniformity is necessary the quantity of the active medicament is within the limit in the formulation.

Ten tablets from each formulation were powdered. The powder equivalent to 150mg of Levofloxacin was weighed and dissolved in Distilled water in 100ml standard flasks. From this suitable dilution was prepared and the solution was analyzed at 298 nm using UV double beam spectrophotometer .

Disintegration time study

The test was carried out on six tablets using distilled water at $37^0C \pm 2^0C$ was used as disintegration media and the time in second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Wetting time study

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. All the post compression parameters results are shown in table 14.

In vitro drug release study

In vitro release studies were carried out by using USP paddle dissolution test apparatus. 900ml of Phosphate buffer (pH 6.8)was taken in the dissolution vessel and the temperature of the medium was maintained at 37±0.5^{o}C. 100rpm was maintained, 1 ml of sample was withdrawn at predetermined time intervals for 0, 1, 3, 6, 9, 12 and 15mints. The same volume of the fresh medium was replaced. The samples were analyzed at 298nm by using a UV spectrophotometer. The dissolution data obtained were plotted as percentage drug release versus time.

FT-IR studies[94]

It was used to study the interactions between the drug and superdisintegrants. The drug and superdisintegrants must be compatible with one another to produce a product stable, efficacious and easy to administer and safe.

IR spectral analysis for drug, superdisintegrants was carried out. If there is no change in peaks of mixture when compared to pure drug, it indicates the absence of interactions.

Stability Studies

The concentration of an active ingredient of any formulation may decrease with increase in temperature and time. This will lead to decrease the potency of the product. Stability study in different temperatures should be carried out to predict the stability of the formulations.

Stability studies were aimed at determining the result of aging and storage under various conditions on the formulated Fast dissolving tablets. Stability studies are used to find out whether any chemical degradation of Levofloxacin formulations take place or not. The formulated tablets were stored at 4^{o}± 2^{o}C (in refrigerator), 27^{o}± 2^{o}C (in room temperature) and 45^{o}C ± 2^{o}C (in accelerated stability chamber) for 45 days. Three tablets were taken from all the stored samples at the intervals of 15th, 30th and 45th days and analysed for drug content and in vitro release studies were carried out to determine the percentage of Levofloxacin released .

9. RESULTS AND DISCUSSIONS

Pre Formulation Studies

The present study was undertaken to formulate Levofloxacin oral dispersible tablets with three polymers namely Crospovidone, CCS and SSG and in combination of three Superdisintegrants and by dry granulation technique. Before compression of the granules physical characters such as, bulk density, tapped density, angle of repose, compressibility index and Hausner ratio were determined and tabulated in the Table12. Then the granules were compressed into tablets and then evaluated. The results are presented in Table 13.

PRECOMPRESSION STUDIES OF GRANULES

Bulk density

The packing properties of the drugs and their formulations widely depend upon bulk density. It has been stated that bulk density values less than 1.2gm/cm^3 indicate good flow and values greater than 1.5 gm/cm^3 indicate poor flow.

From the results it can be seen that the bulk density values are less than 1.2gm/cm^3. This indicates good flow characteristics of the granules. Values showed Table No.12.

Tapped density

From the above results it can be seen that the Tapped density values indicate good flow characteristics of the granules. Values showed Table No.12.

Angle of Repose

Angle of repose less than or equal to 40^oC indicates free flowing properties of thegranules. However angle of repose greater than 40^oCindicates poor flow of material.

It can be observed from above table that the angle of repose for various batches of thegranules is found to be less than 40^{o}C, it indicates good flow properties of the granules. Values showed Table No.12.

Compressibility Index or Carr's Index

Carr's Index less than or equal to <10 indicates free flowing properties of the granules. However Carr's Index greater than <10 indicates poor flow of material.

It can be observed from above table that the Carr's Index for various batches of thegranules is found to be less than >10; it indicates good flow properties of the granules. Values showed Table No.12.

Hausner's Ratio

Hausner's Ratio less than or equal to 1.069 indicates free flowing properties of thegranules. However Hausner's Ratio greater than 1.35 indicates poor flow of material.

It can be observed from above table that the Hausner's Ratio for various batches of the granules is found to be less than 1.122; it indicates good flow properties of the granules.

Table no – 12 :Precompression studies of powder blend

S. No	Formulations	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of Repose (θ)	Carr's Index (%)	Hausner's Ratio
1	FLOT-1	0.334	0.375	32.26	10.93	1.122
2	FLOT-2	0.346	0.372	34.15	6.98	1.075
3	FLOT-3	0.328	0.362	33.82	9.39	1.103
4	FLOT-4	0.312	0.333	31.38	6.30	1.067
5	FLOT-5	0.333	0.368	35.07	9.51	1.105
6	FLOT-6	0.352	0.384	35.07	8.33	1.090
7	FLOT-7	0.326	0.354	39.48	7.90	1.085

EVALUATION OF LEVOFLOXACIN ORAL DISPERSIBLE TABLETS

The compressed tablets were evaluated for physical properties and the results are tabulated in Table no -13

Hardness Test

The hardness of the tablet various batches were determined. The various batches of the tablets of hardness values are found within limits and it indicates good strength of the oral dispersible tablets. Values showed Table. No 13.

Thickness Test

The tablets mean thicknesses were almost uniform in the all formulations and were found to be in the range of 0.37mm. Values showed Table. No 13.

Friability Test

The oral dispersibletablets friability values are found to be less than 1% in all cases and considered to be satisfactory. Values showed Table. No 13.

Weight variation test

All this oral dispersibletablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weight of the all tablets was found to be uniform with low standard deviation values. Values showed Table. No 13.

Estimation of Drug Content

Drug content of all the batches are within the acceptable range which shows the proper mixing of the drug with the excipients. Values showed Table. No 13.

Disintegration time study

The disintegration time (D.T) of all formulations is shown in the Table No.14 and Figure No.8.

Table No.13: Postcompression studies of Levofloxacin oral dispersible Tablets

S. No	Formulations	Hardness Test (kg/cm)	Thickness Test (cm)	Friability Test (%)	% of Weight variation test	Estimation of Drug Content %
1	FLOT-1	2.45	0.37	0.164	99.7	98.12
2	FLOT-2	2.34	0.37	0.228	99.2	96.29
3	FLOT-3	3.42	0.37	0.236	99.8	97.54
4	FLOT-4	2.92	0.37	0.267	99.8	97.27
5	FLOT-5	2.65	0.37	0.224	99.6	96.48
6	FLOT-6	3.23	0.37	0.254	99.5	98.34
7	FLOT-7	2.86	0.37	0.253	99.9	98.84

Table No.14: Postcompression studies of Levofloxacin oral dispersible Tablets

S.No	Formulations	Disintegration time (sec)	Wetting time(sec)
1	FLOT-1	25	17
2	FLOT-2	23	16
3	FLOT-3	32	17
4	FLOT-4	22	15
5	FLOT-5	25	15
6	FLOT-6	23	16
7	FLOT-7	20	14

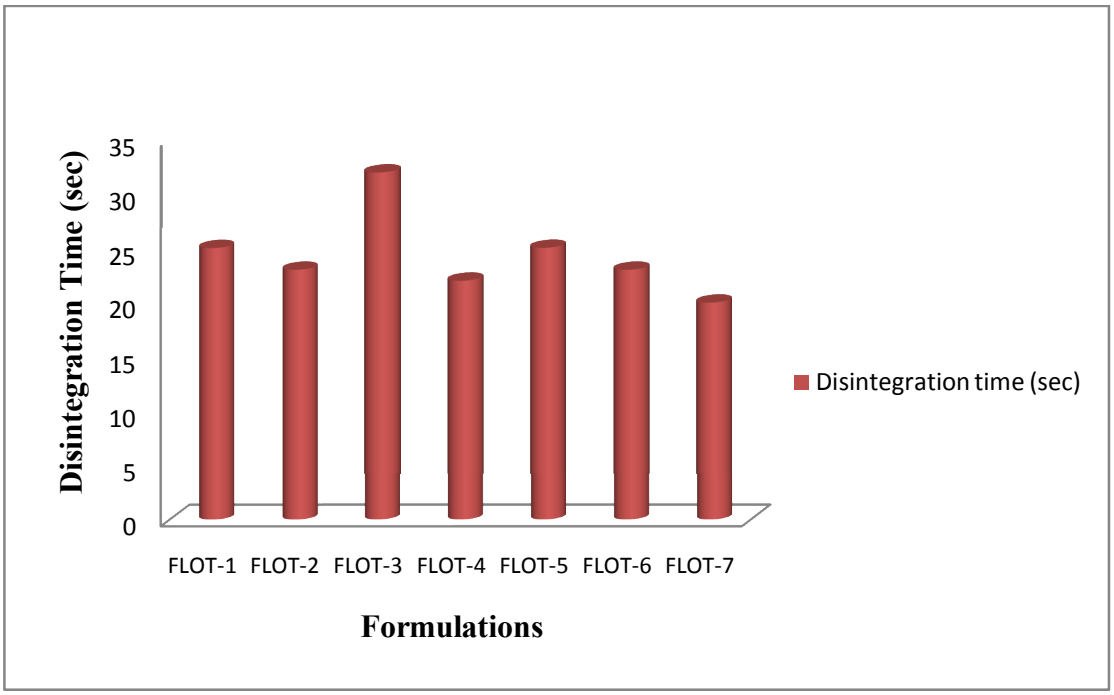


Figure no – 8 :Disintegration time

Wetting time study

The wetting time (W.T) of all formulations is shown in the Table No.14.

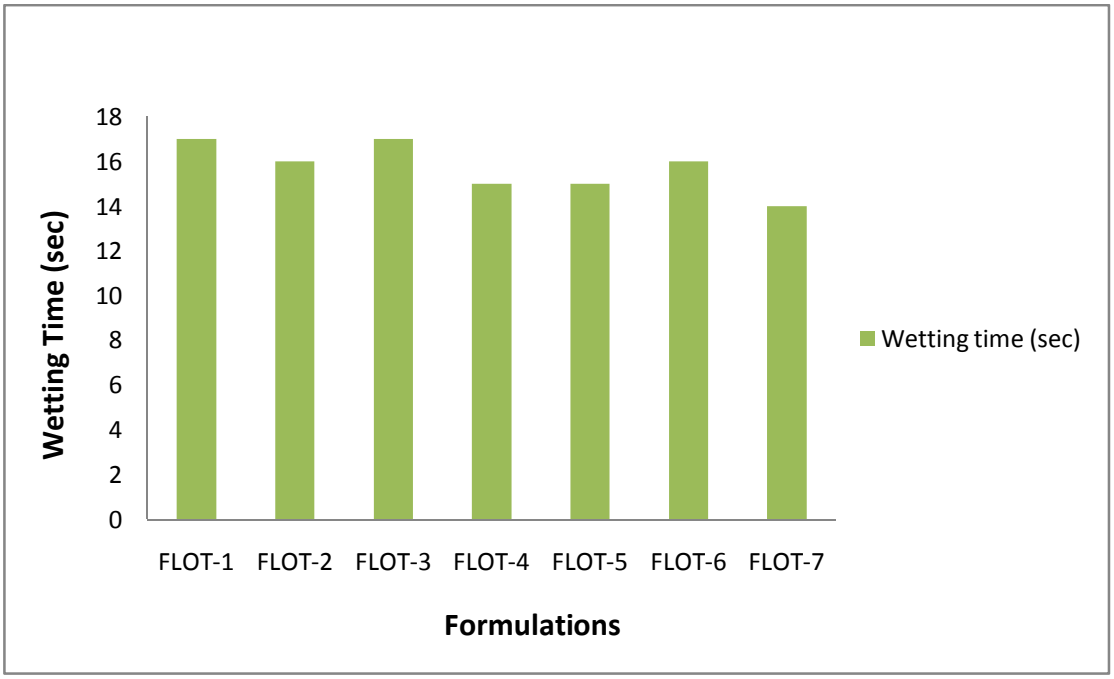


Figure no – 9 :Wetting time

IR Spectral analysis

The IR Spectral studies of Pure levofloxacine, Crospovidone, Sodium starch glycolate and CCS were carried out to study the interaction between the drug and super disintegrants used.It showed that IR spectrum of pure Levofloxacin and superdisintegrants were similar fundamental peaks and patterns. The results proved that there were no significant interactions between the drug and super disintegrants. The results are shown in Figures:10 - 20**.**

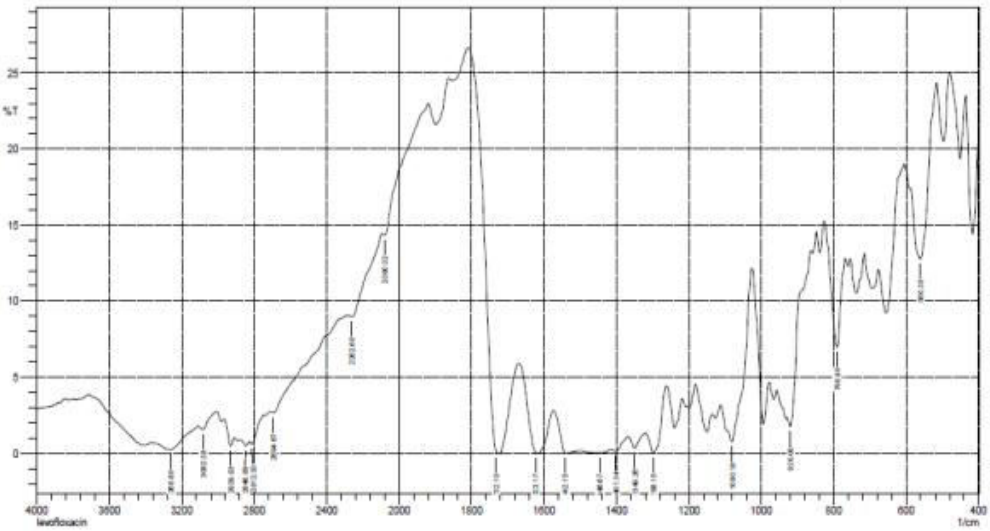


Figure No.10: FTIR spectrum of Levofloxacin

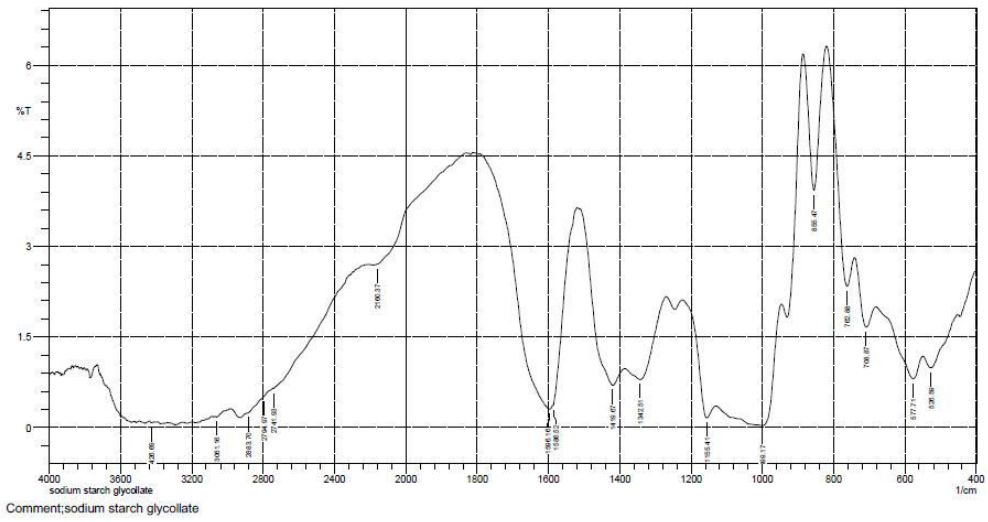


Figure No.11: FTIR spectrum of SSG

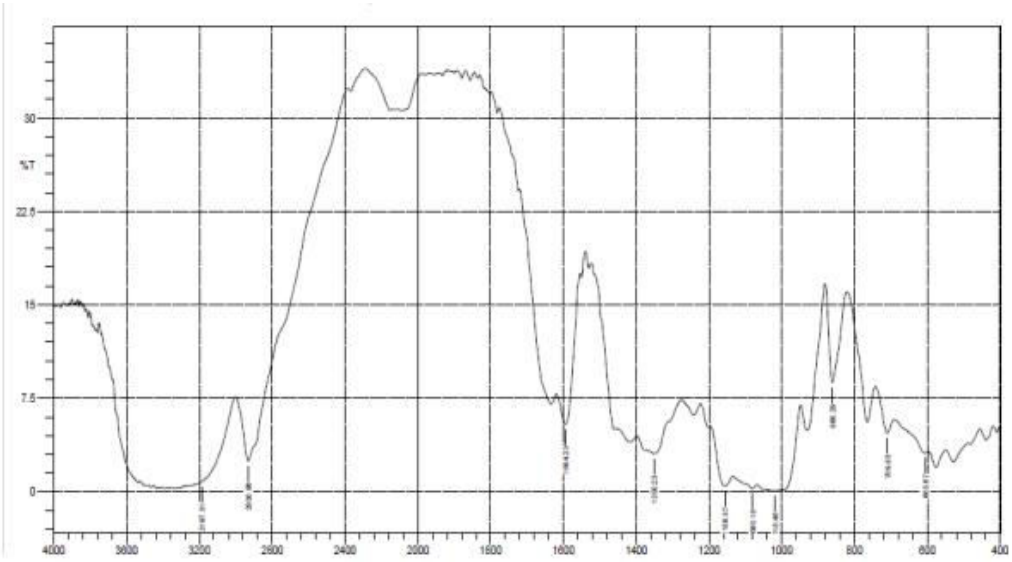


Figure No.12: FTIR spectrum of CCS

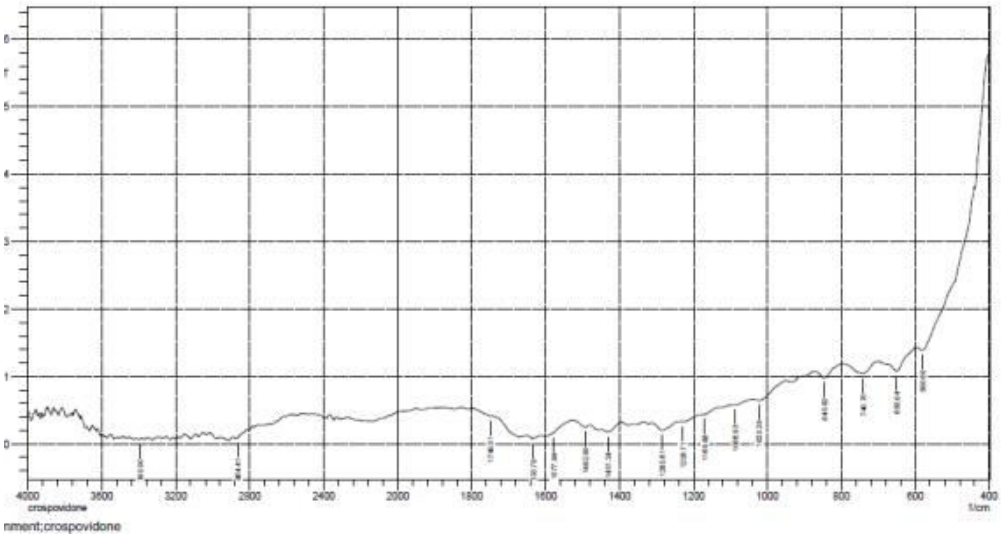


Figure No.13: FTIR spectrum of CP

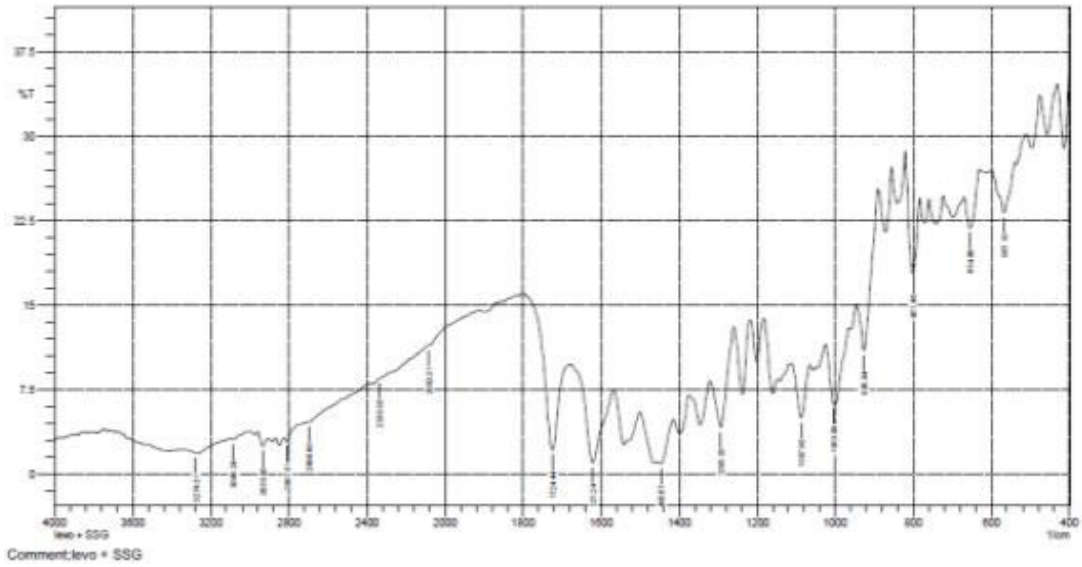


Figure No.14: FTIR spectrum of Levofloxacin and SSG

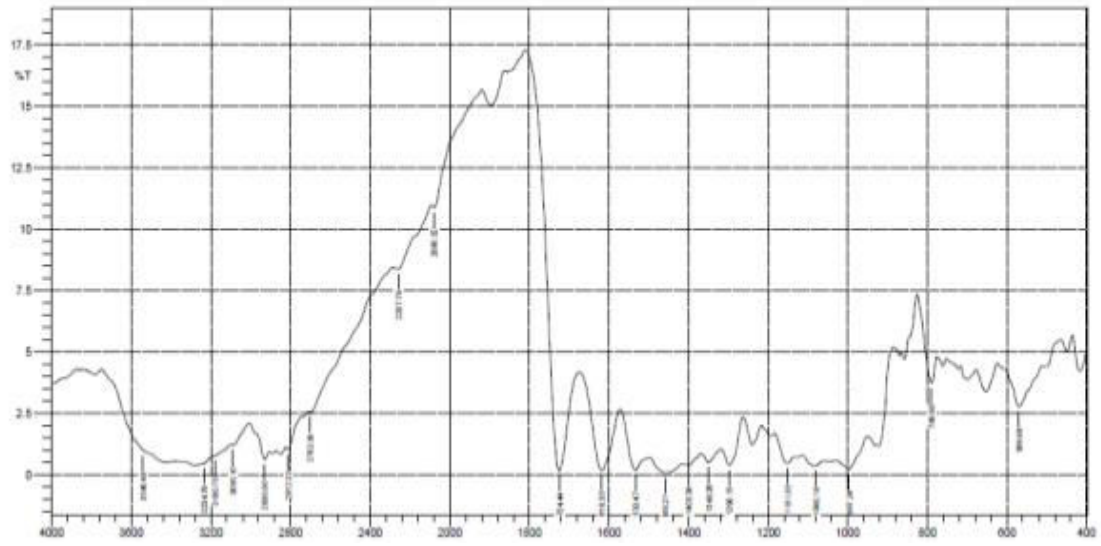


Figure No.15: FTIR spectrum of Levofloxacin and CCS

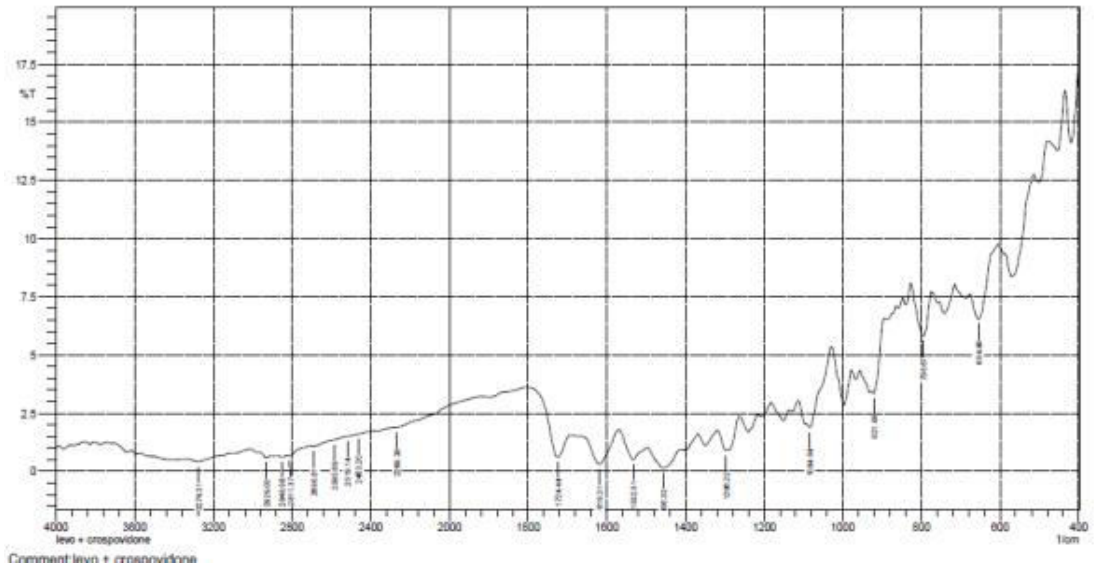


Figure No.16: FTIR spectrum of Levofloxacin and CP

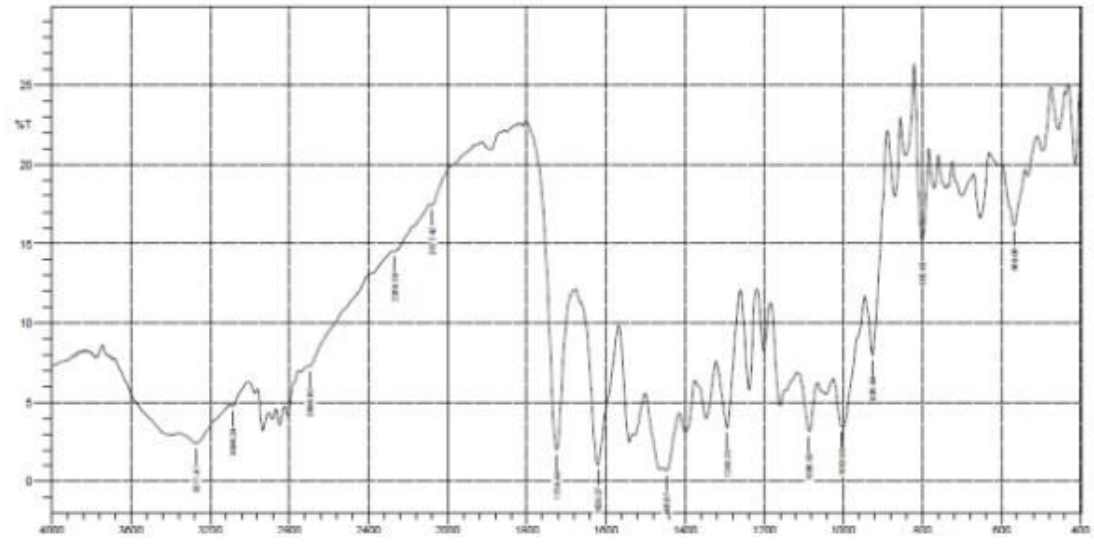


Figure No.17: FTIR spectrum of Levofloxacin +SSG+CCS

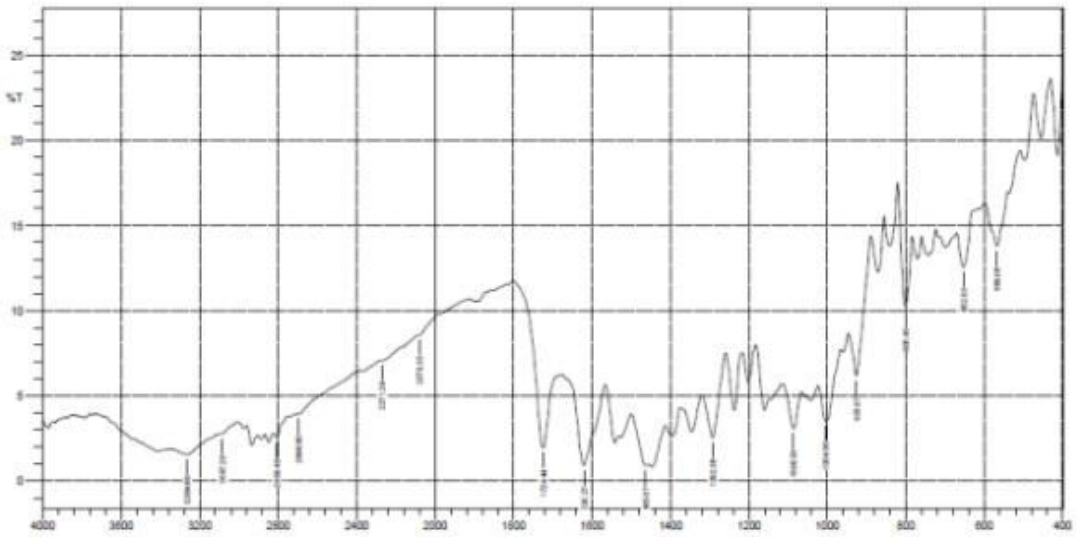


Figure No.18: FTIR spectrum of Levofloxacin +CCS+CP

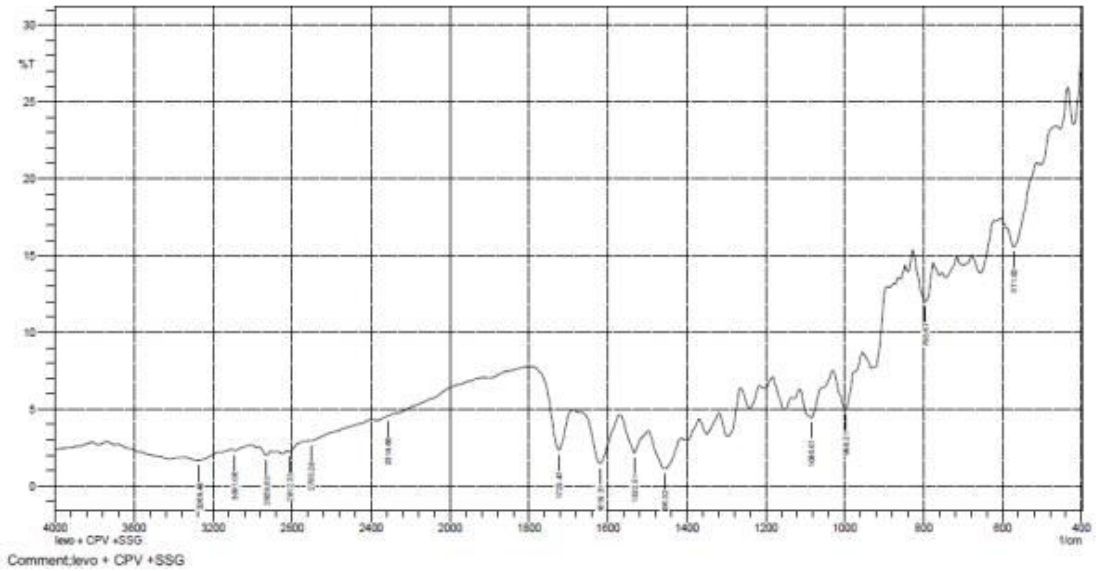


Figure No.19: FTIR spectrum of Levofloxacin +SSG+CP

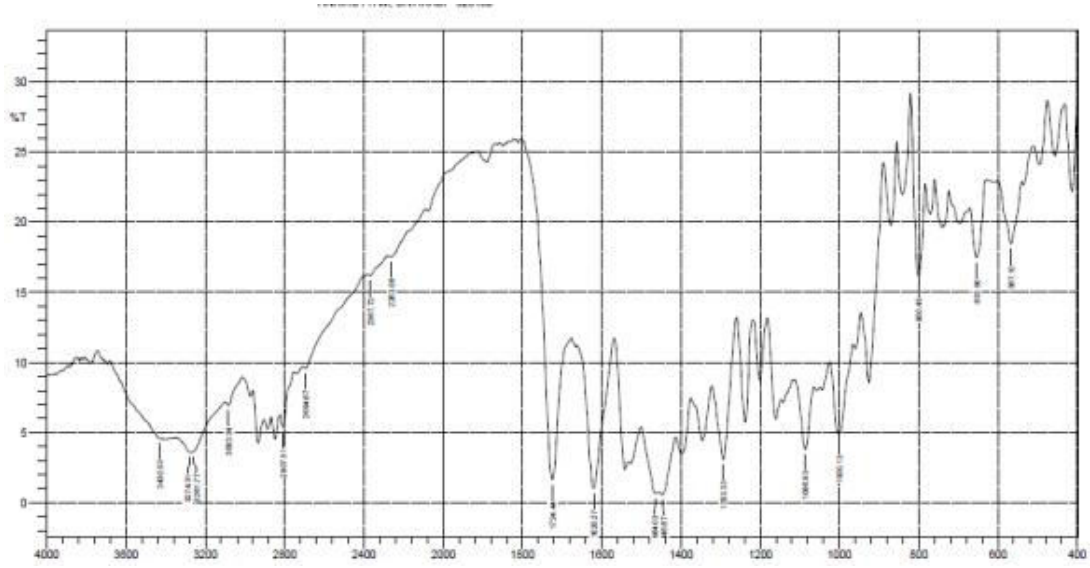


Figure No.20: FTIR spectrum of Levofloxacin +SSG+CCS+CP

IN-VITRO DRUG RELEASE STUDY

Tablets of all the formulations were subjected for *invitro* release studies .the results are presented in Table no. (21-28).

Table No.15: Formulations-1 (FLOT-1)

S. No	Time (mints)	Absorbance (298nm)	Concentration (µg/ml)	Amount of drug release (in 900 ml)	% of drug release
1	0	0.000	0.000	0.000	0.000
2	1	0.125	1.078	9.710	6.47
3	3	0.496	4.350	39.15	26.61
4	6	0.684	6.000	54.00	36.00
5	9	0.923	8.096	72.86	48.57
6	12	1.249	10.956	98.605	65.73
7	15	1.723	15.114	136.02	90.68

Figure No.21:Formulations-1(FLOT-1)

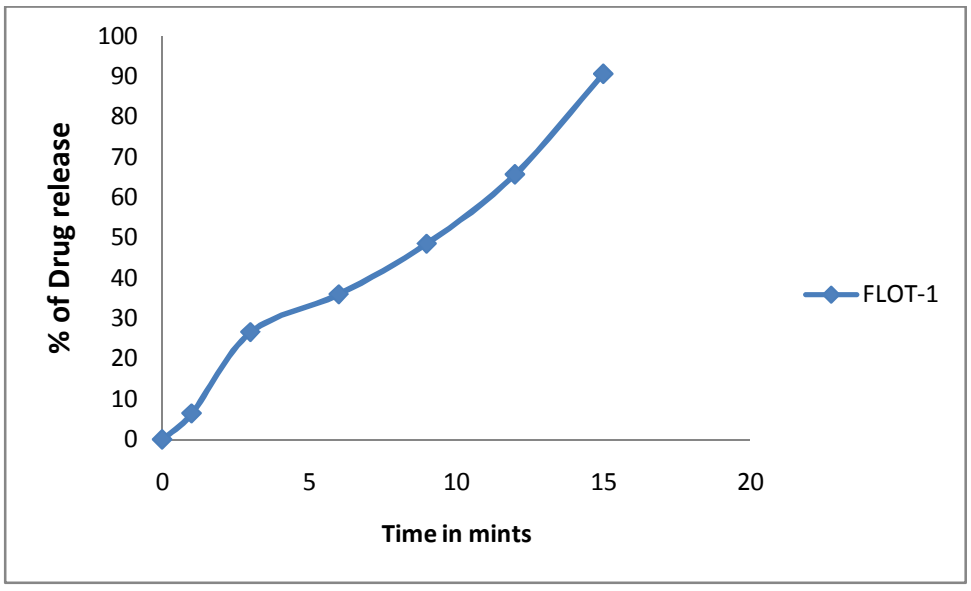


Table No.16: Formulations-2 (FLOT-2)

S. No	Time (mints)	Absorbance (298nm)	Concentration (µg/ml)	Amount of drug release (in 900 ml)	% of drug release
1	0	0.000	0.000	0.000	0.000
2	1	0.096	0.842	7.578	5.05
3	3	0.392	3.438	30.94	20.63
4	6	0.592	5.192	46.73	31.15
5	9	0.879	7.710	69.39	46.26
6	12	1.152	10.10	90.94	60.63
7	15	1.674	14.68	132.1	88.10

Figure No.22: Formulation-2 (FLOT-2)

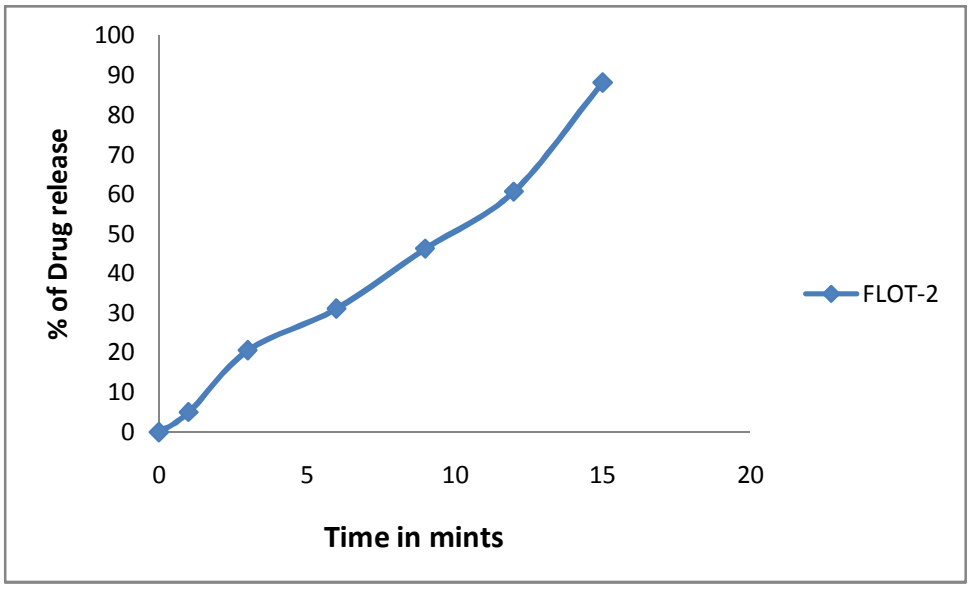


Table No.17: Formulations-3 (FLOT-3)

S. No	Time (mints)	Absorbance (298nm)	Concentration (µg/ml)	Amount of drug release (in 900 ml)	% of drug release
1	0	0.000	0.000	0.000	0.000
2	1	0.082	0.719	6.473	4.315
3	3	0.364	3.192	28.73	19.15
4	6	0.562	4.929	44.36	29.57
5	9	0.853	7.482	67.34	44.89
6	12	1.106	9.701	87.31	58.21
7	15	1.583	13.88	124.9	83.31

Figure No.23:Formulations-3 (FLOT-3)

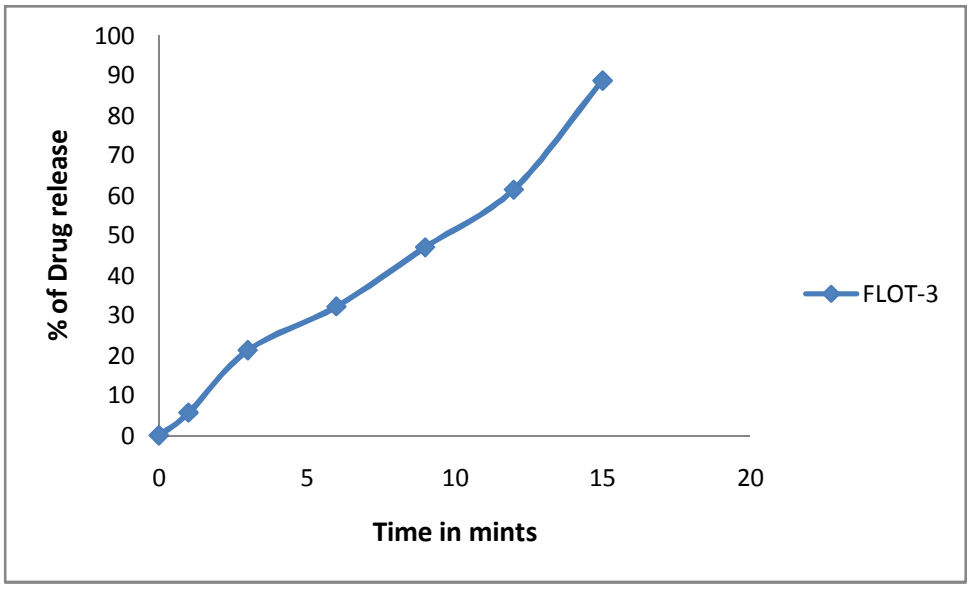


Table No.18: Formulations-4 (FLOT-4)

S. No	Time (mints)	Absorbance (298nm)	Concentration (µg/ml)	Amount of drug release (in 900 ml)	% of drug release
1	0	0.000	0.000	0.000	0.000
2	1	0.132	1.157	10.42	6.947
3	3	0.521	4.570	41.13	27.42
4	6	0.694	6.087	54.78	36.52
5	9	0.942	8.263	74.36	49.57
6	12	1.256	11.01	99.15	66.10
7	15	1.763	15.46	139.1	92.78

Figure No.24:Formulations-4 (FLOT-4)

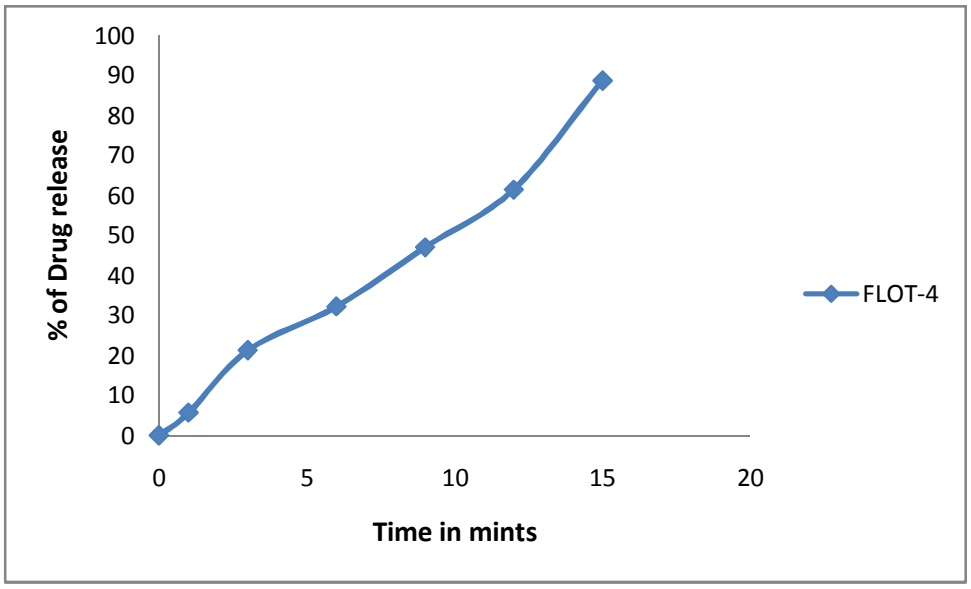


Table No.19: Formulations-5 (FLOT-5)

S. No	Time (mints)	Absorbance (298nm)	Concentration (µg/ml)	Amount of drug release (in 900 ml)	% of drug release
1	0	0.000	0.000	0.000	0.000
2	1	0.108	0.947	8.526	5.684
3	3	0.405	3.552	31.97	21.31
4	6	0.612	5.368	48.31	32.21
5	9	0.894	7.842	70.57	47.05
6	12	1.168	10.24	92.21	61.47
7	15	1.686	14.78	133.1	88.73

Figure No.25:Formulations-5 (FLOT-5)

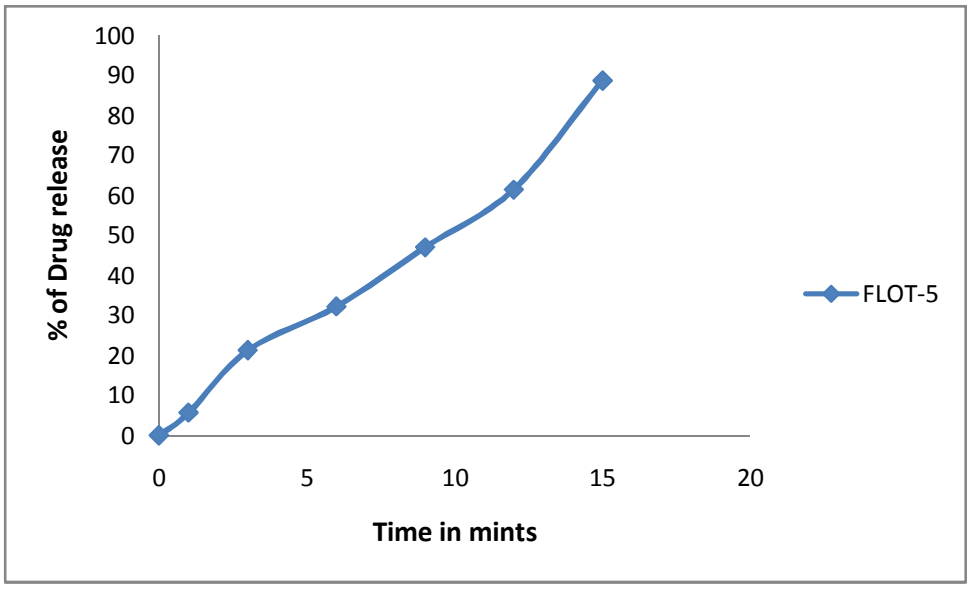


Table No.20: Formulations-6 (FLOT-6)

S. No	Time (mints)	Absorbance (298nm)	Concentration (µg/ml)	Amount of drug release (in 900 ml)	% of drug release
1	0	0.000	0.000	0.000	0.000
2	1	0.128	1.122	10.10	6.736
3	3	0.514	4.508	40.57	27.05
4	6	0.674	5.912	53.21	35.47
5	9	0.926	8.122	73.10	48.73
6	12	1.235	10.83	97.50	65.00
7	15	1.745	15.30	137.7	91.84

Figure No.26:Formulations-6 (FLOT-6)

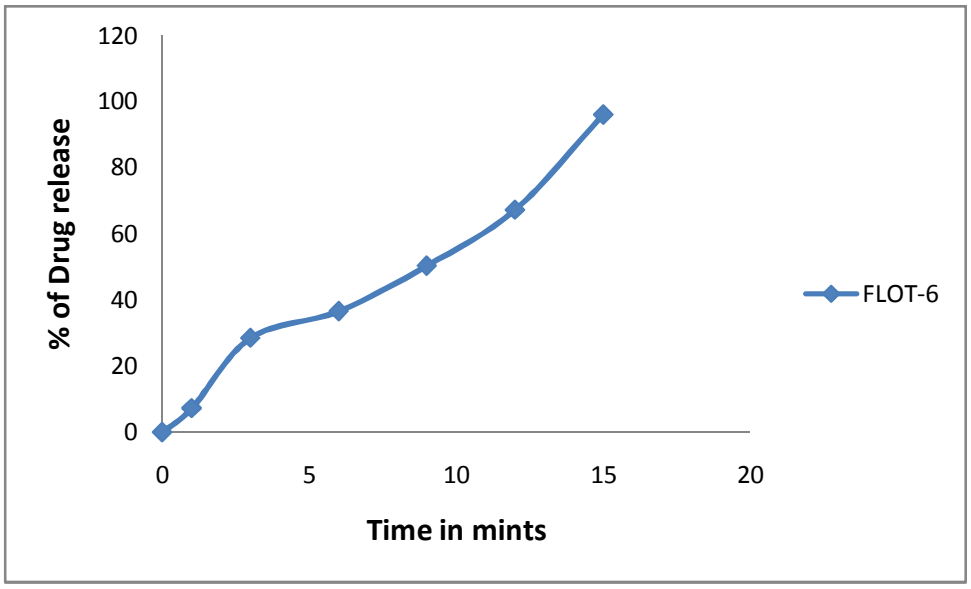


Table No.21: Formulations-7 (FLOT-7)

S. No	Time (mints)	Absorbance (298nm)	Concentration (µg/ml)	Amount of drug release (in 900 ml)	% of drug release
1	0	0.000	0.000	0.000	0.000
2	1	0.138	1.210	10.89	7.263
3	3	0.542	4.754	42.78	28.52
4	6	0.696	6.105	54.94	36.63
5	9	0.957	8.394	75.55	50.36
6	12	1.278	11.21	100.8	67.26
7	15	1.826	16.01	144.1	**96.10**

Figure No.27:Formulations-7 (FLOT-7)

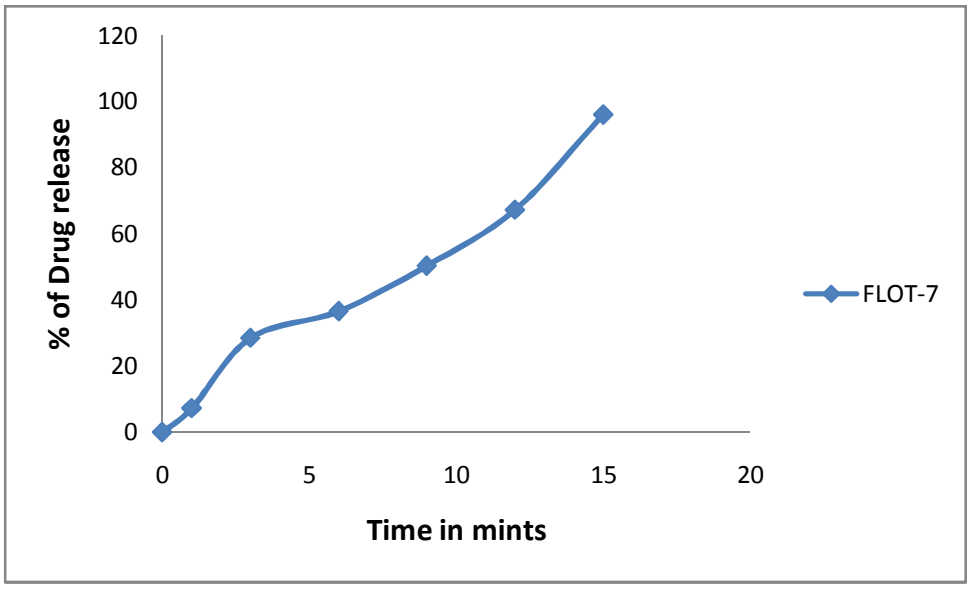


Table No.22:Comparative dissolution study of different formulations with various ratios of Super disintegrants

S. No	Time (mints)	% of drug release (FLOT-1)	% of drug release (FLOT-2)	% of drug release (FLOT-3)	% of drug release (FLOT-4)	% of drug release (FLOT-5)	% of drug release (FLOT-6)	% of drug release (FLOT-7)
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	6.47	5.05	4.315	6.947	5.684	6.736	7.263
3	3	26.61	20.63	19.15	27.42	21.31	27.05	28.52
4	6	36.00	31.15	29.57	36.52	32.21	35.47	36.63
5	9	48.57	46.26	44.89	49.57	47.05	48.73	50.36
6	12	65.73	60.63	58.21	66.10	61.47	65.00	67.26
7	15	90.68	88.10	83.31	92.78	88.73	91.84	96.10

Figure No.28A: Comparative dissolution study of different formulations with various ratios of polymers

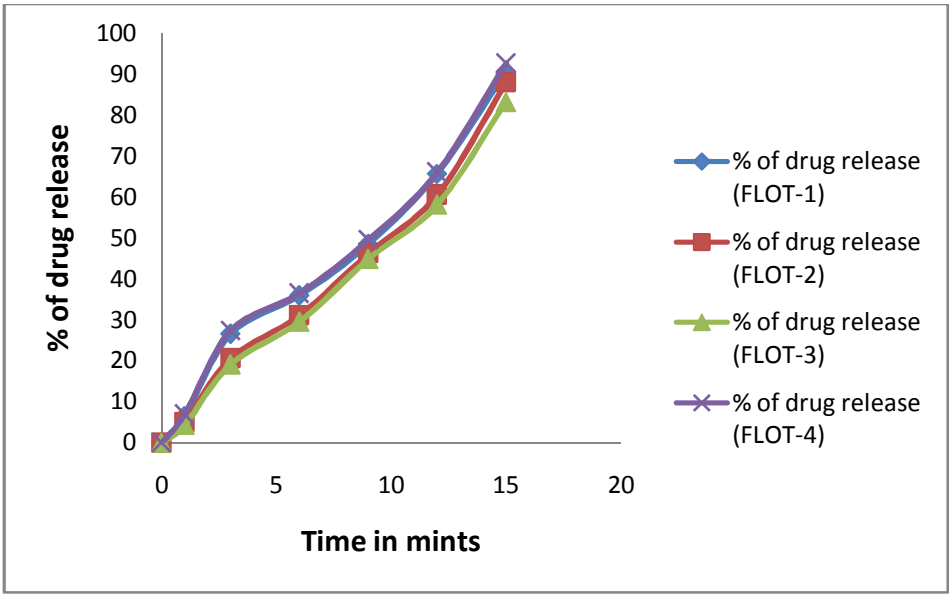
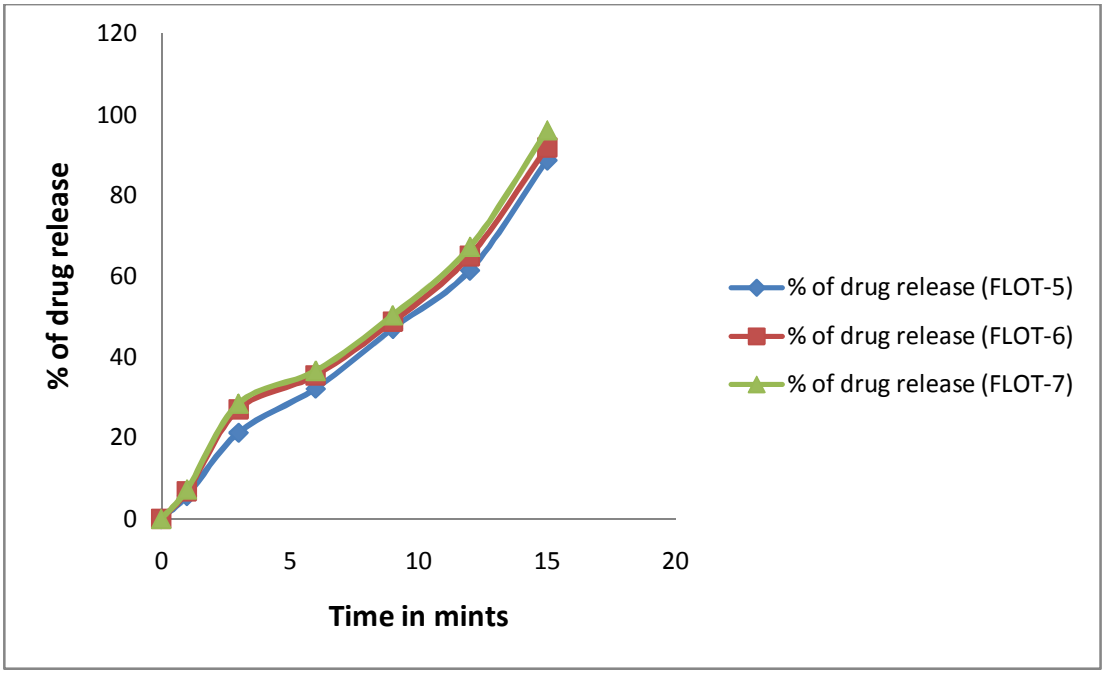


Figure No.28 (B): Comparative dissolution study of different formulations with various ratios of Super disintegrants



STABILITY STUDIES

Levofloxacin oral dispersible tablets (all 7 formulations) were stored at refrigerated temperature (4°C±2°C), room temperature (27°C± 2°C) and in programmable envirnomental test chamber (45°C± 2°C) for 45 days.

At the end of 15, 30 and 45 days of storage, the controlled release tablets were observed for changes in physical appearance analyzed for drug content and subjected to *invitro* release studies and the result was presented in Table No 23 - 30

There was no change in the percentage release of Levofloxacin from all the formulations stored at different temperatures upto 45 days. Tablet evaluation tests were carried out and there were no deviations in all the tests and all are within the limits. It showed that all the formulations are physically stable. There was no change in the drug content Table No23 and *invitro* drug release Table No 24-30. It showed that all the formulations are chemically stable.

Table No -23

DRUG CONTENT ESTIMATION AFTER STORING AT DIFFERENT TEMPERATURES

No	Formulation	DRUG CONTENT*								
		$4^{O}C\pm 2^{O}C$			$27^{O}C\pm 2^{O}C$			$45^{O}C\pm 2^{O}C$		
		15th days	30th days	45th days	15th days	30th days	45th days	15th days	30th days	45th days
1	F1	98.12	98.11	98.14	98.10	98.11	98.12	98.13	98.15	98.12
2	F2	96.29	96.27	96.28	96.31	96.31	96.30	96.29	96.28	96.27
3	F3	97.54	97.56	97.53	97.52	97.51	97.55	97.54	97.52	97.54
4	F4	97.27	97.28	97.24	97.28	97.29	97.24	97.28	97.24	97.27
5	F5	96.48	96.49	96.47	96.45	96.45	96.46	96.48	96.49	96.48
6	F6	98.34	98.32	98.31	98.34	98.33	98.35	98.32	98.34	98.35
7	F7	98.84	98.85	98.87	98.82	98.83	98.81	98.85	98.86	98.84

Table No –24

STABILITY STUDIES OF DISSOLUTION PROFILE OF FORMULATION –F1

S.No	Time in (mts)	0 days	PERCENTAGE DRUG RELEASE (%)*								
			15th days			30th days			45th days		
			4°C± 2°C	27°C ± 2°C	45°C± 2°C	4° C± 2°C	27°C± 2° C	45°C± 2°C	4°C± 2°C	27°C± 2° C	45°C± 2°C
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	6.47	6.44	6.46	6.45	6.48	6.47	6.49	6.44	6.48	6.45
3	3	26.61	26.64	26.62	26.63	26.59	26.60	26.62	26.63	26.64	26.61
4	6	36.00	36.01	36.03	36.02	36.01	36.04	36.02	36.04	36.00	36.05
5	9	48.57	48.59	48.57	48.58	48.55	48.56	48.57	48.54	48.59	48.58
6	12	65.73	65.72	65.71	65.74	65.72	65.73	65.76	65.75	65.74	65.73
7	15	90.68	90.69	90.68	90.70	90.66	90.65	90.68	90.69	90.69	90.67

Table No- 25

STABILITY STUDIES OF DISSOLUTION PROFILE OF FORMULATION –F2

S. No	Time in (mts)	0 days	PERCENTAGE DRUG RELEASE (%)*								
			15th days			30th days			45th days		
			4°C± 2°C	27°C ± 2°C	45°C± 2°C	4° C± 2°C	27°C± 2° C	45°C± 2°C	4°C± 2°C	27°C± 2° C	45°C± 2°C
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	5.05	5.04	5.06	5.03	5.02	5.07	5.05	5.04	5.07	5.05
3	3	20.63	20.62	20.61	20.64	20.61	20.65	20.63	20.64	20.62	20.63
4	6	31.15	31.12	31.14	31.16	31.17	31.14	31.16	31.15	31.14	31.12
5	9	46.26	46.28	46.26	46.25	46.22	46.23	46.24	46.25	46.28	46.27
6	12	60.63	60.61	60.62	60.65	60.66	60.61	60.62	60.63	60.64	60.63
7	15	88.10	88.11	88.12	88.10	88.09	88.08	88.11	88.12	88.01	88.10

Table No –26

STABILITY STUDIES OF DISSOLUTION PROFILE OF FORMULATION –F3

S.No	Time in (mts)	0 days	PERCENTAGE DRUG RELEASE (%)*								
			15th days			30th days			45th days		
			4°C± 2°C	27°C ± 2°C	45°C± 2°C	4°C± 2°C	27°C± 2° C	45°C± 2°C	4°C± 2°C	27°C± 2° C	45°C± 2°C
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	4.315	4.320	4.318	4.316	4.312	4.310	4.314	4.313	4.312	4.315
3	3	19.15	19.16	19.15	19.14	19.11	19.12	19.16	19.18	19.15	19.12
4	6	29.57	29.54	29.53	29.56	29.58	29.59	29.58	29.56	29.57	29.58
5	9	44.89	44.88	44.87	44.84	44.90	44.91	44.84	44.86	44.85	44.89
6	12	58.21	58.19	58.20	58.26	58.25	58.25	58.23	58.20	58.24	58.22
7	15	83.31	83.29	83.28	83.32	83.33	83.31	83.34	83.33	83.35	83.34

Table No – 27

STABILITY STUDIES OF DISSOLUTION PROFILE OF FORMULATION –F4

S.No	Time in (mints)	0 days	PERCENTAGE DRUG RELEASE (%)*								
			15th days			30th days			45th days		
			4°C± 2°C	27°C ± 2°C	45°C± 2°C	4° C± 2°C	27°C± 2°C	45°C± 2°C	4°C± 2°C	27°C± 2°C	45°C± 2°C
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	6.947	6.942	6.945	6.945	6.942	6.939	6.940	6.944	6.949	6.947
3	3	27.42	27.41	27.40	27.41	27.43	27.42	27.49	27.45	27.41	27.43
4	6	36.52	36.53	36.53	36.50	36.51	36.55	36.54	36.53	36.51	36.54
5	9	49.57	49.56	49.58	49.57	49.56	49.52	49.53	49.58	49.59	49.56
6	12	66.10	66.13	66.12	66.11	66.10	66.09	66.14	66.11	66.13	66.15
7	15	92.78	92.79	92.78	92.77	92.80	92.78	92.77	92.76	92.75	92.74

Table No - 28

STABILITY STUDIES OF DISSOLUTION PROFILE OF FORMULATION –F5

S.No	Time in (mts)	0 days	PERCENTAGE DRUG RELEASE (%)*								
			15th days			30th days			45th days		
			4°C± 2°C	27°C ± 2°C	45°C± 2°C	4° C± 2°C	27°C± 2°C	45°C± 2°C	4°C± 2°C	27°C± 2°C	45°C± 2°C
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	5.684	5.682	5.679	5.646	5.684	5.676	5.682	5.681	5.680	5.683
3	3	21.31	21.32	21.34	21.33	21.35	21.28	21.31	21.30	21.33	21.32
4	6	32.21	32.22	32.23	32.20	32.19	32.24	32.23	32.21	32.22	32.19
5	9	47.05	47.04	47.06	47.02	47.01	47.03	47.07	47.08	47.09	47.05
6	12	61.47	61.42	61.46	61.48	61.46	61.44	61.43	61.47	61.48	61.49
7	15	88.73	88.74	88.76	88.75	88.71	88.72	88.73	88.74	88.76	88.77

Table No – 29

STABILITY STUDIES OF DISSOLUTION PROFILE OF FORMULATION –F6

S.No	Time in (mts)	0 days	PERCENTAGE DRUG RELEASE (%)*								
			15th days			30th days			45th days		
			4°C± 2°C	27°C ± 2°C	45°C± 2°C	4° C± 2°C	27°C± 2°C	45°C± 2°C	4°C± 2°C	27°C± 2°C	45°C± 2°C
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	6.736	6.745	6.732	6.754	6.727	6.721	6.741	6.752	6.736	6.739
3	3	27.05	27.04	27.06	27.03	27.01	27.04	27.06	27.04	27.05	27.01
4	6	35.47	35.44	35.48	35.49	35.47	35.46	35.46	35.48	35.44	35.49
5	9	48.73	48.72	48.76	48.77	48.75	48.76	48.73	48.72	48.71	48.75
6	12	65.00	65.02	65.05	65.02	65.00	65.01	65.02	65.03	65.04	65.01
7	15	91.84	91.83	91.85	91.86	91.82	91.82	91.86	91.87	91.83	91.82

Table No - 30

STABILITY STUDIES OF DISOLUTION PROFILE OF FORMULATION –F7

S.No	Time in (mts)	0 days	PERCENTAGE DRUG RELEASE (%)*								
			15th days			30th days			45th days		
			4°C± 2°C	27°C ± 2°C	45°C± 2°C	4°C± 2°C	27°C± 2°C	45°C± 2°C	4°C± 2°C	27°C± 2°C	45°C± 2°C
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	7.263	7.252	7.251	7.268	7.272	7.282	7.264	7.263	7.268	7.262
3	3	28.52	28.51	28.53	28.52	28.54	28.51	28.54	28.56	28.58	28.55
4	6	36.63	36.61	36.62	36.63	36.65	36.66	36.64	36.64	36.62	36.61
5	9	50.36	50.32	50.38	50.37	50.34	50.33	50.36	50.31	50.32	50.34
6	12	67.26	67.24	67.26	67.28	67.27	67.25	67.24	67.29	67.28	67.26
7	15	96.10	96.18	96.10	96.09	96.10	96.11	96.12	96.14	96.17	96.18

DISCUSSION

Oral dispersible tablets of Levofloxacin were prepared by directcompression method. The prepared Oral dispersible tablets are round in shape. Microscopic examination of tablets from each formulation batch showed circular shape with no cracks. The fourier transform infra-red analysis was conducted for the surface structure characterization. FTIR spectrum of the formulated Oral dispersible tablets, pure drug and super disintegrants was recorded. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the super disintegrants and pure drug.

Bulk density (0.312 to 0.352 gm/cm^3) and Tapped density (0.333 to 0.384 gm/cm^3) values are within the limits, indicating that the powder blends have the required flow property for direct compression. The values obtained for angle of repose for all formulations are tabulated in table the values were found to be in the range from 31.38-39.48^{0}C. This indicates good flow property of the powder blend. Compressibility index (6.30 to 10.93) and Hausner's ratio (1.067 to 1.122) values are within the limits, indicating that the powder blends have the required flow property for direct compression.

The hardness of the Oral dispersible tablet various batches were determined. The various batches of the Oral dispersible tablets of hardness values are found within limits and it indicates good strength of the Oral dispersible tablets. Tablet mean thicknesses were almost uniform in the all formulations and were found to be in the range of 0.37mm. Friability values are found to be less than 1% in all cases and considered to be satisfactory. All this tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. Drug content of all the batches are within the acceptable range which shows the proper mixing of the drug with the excipients.

The *in vitro* drug release profile of tablets from each batch (FLOT-1 to FLOT-7) was carried in phosphate buffer (pH 6.8) for 15 mints by using paddle type of device. From the *in vitro* dissolution data, FLOT-7 formulation was found that the drug release is best and the cumulative % of drug release was 96.10 % respectively, when compared to other formulation.

All the formulations were subjected for stability studies for 45 days at different temperatures such as room temperature, fridge temperature and acclerated temperature (45°C±2°C). At 15 days interval upto 45 days, the drug content and dissolution studies were carried out. There was no significant change in the drug content and *invitro* drug release.

9. SUMMARY AND CONCLUSION

Oral dispersible Tablets of Levofloxacin were prepared with two different superdisintegrants and evaluation of blend powder, tablets evaluation studies, IR spectral studies, dissolution studies and stability studies were performed .The summary are presented.

- Preformulation studies such as angle of repose, bulk density, tapped density, compressibility index and hausner ratio were performed and the results showed that all the parameters are within the acceptable limits.
- Tablets were prepared by direct compression method and evaluated for general appearance, hardness test, uniformity of weight, friability, wetting time, disintegration time, drug content estimation and in vitro release study. All the formulations were found to be good appearance without showing any chipping, capping and sticking defects and all other parameters were passed the test.
- IR spectroscopic studies indicated that the drug is compatible with all the polymers and there was no drug-polymer interaction.
- When comparing all the formulations, F7 shows a better drug release of **96.10%** at the end of 15 minutes.
- All the formulations were subjected for stability studies for 45 days at different temperatures such as room temperature, fridge temperature and accelerated temperature (45°C±2°C). At 15 days interval upto 45 days, the drug content and dissolution studies were carried out. There was no significant change in the drug content and *invitro* drug release.

The main objective of the present study was to develop Oral dispersible tablet formulation containing 150mg of Levofloxacin for the treatment of a number of infections including infection of Joints and bones, respiratory tract infections, urinary tract infections, skin structural infections and typhoid fever etc. In the present work it has been observed from all formulations of precompression and post compression studies were given within the limit of values. The *in vitro* dissolution data, FLOT-7(combination of different superdisintegrants) formulation was found that the drug release is best and the cumulative % of drug release was 96.10 % respectively, when compared to other formulation.

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